I. Katona

Arthritis Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research

December 1, 1998

Town Center Hotel
8727 Colesville Road, Silver Spring, MD

NDA 20-998, Celebrex ™, (celecoxib), Searle

Contents

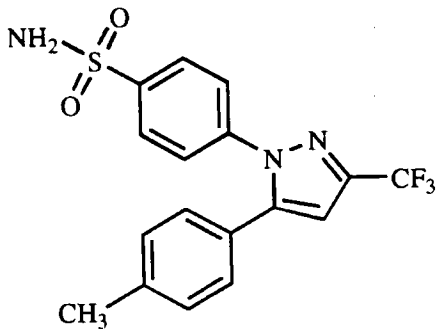
Agenda and Questions

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW DRAFT

NDA: 20-998 **SUBMISSION DATES:** 6/29/98,
PRODUCT: Celebrex™ (celecoxib) Capsules, 100 mg & 200 mg 8/24/98, 9/3/98, 10/1/98
SPONSOR: Searle
4901 Searle Parkway
Skokie, IL 60077
TYPE OF SUBMISSION: Original, 1P **REVIEWER:** Sue-Chih Lee, Ph.D.

1. Synopsis

Celecoxib (SC-58635), a diarylsubstituted pyrazole compound, is a member of a novel class of agents that selectively inhibits cyclooxygenase-2 (COX-2). It is intended for use as an oral anti-inflammatory and analgesic agent for the acute or chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and management of pain.



In support of this application, the sponsor has submitted a total of 30 pharmacokinetic studies. Out of these, 2 studies (one single dose and one multiple dose studies) were conducted in Japanese healthy subjects and were not reviewed in full length because they did not add new information to this application. It was noted that results from additional studies were used to support the labeling and were included in the summary section but the individual reports were not provided in Section 6. This reviewer has since requested and reviewed these individual reports except for the study in renal insufficiency patients which is currently under review. The following is a brief summary of the pharmacokinetic study results.

Pharmacokinetic characteristics of celecoxib

Absorption: Following a single dose under fasted conditions, peak plasma celecoxib concentrations (Cmax for a 200 mg dose) occur at approximately 3 hours postdose. Relative to an oral suspension, Celebrex capsules have a relative bioavailability of 99%. Because of the low aqueous solubility of celecoxib, absolute bioavailability studies have not been conducted. Multiple dose pharmacokinetics of celecoxib can generally be predicted from the single dose pharmacokinetics.

Effects of food and antacid: When Celebrex capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in Cmax of and total absorption (AUC) of (for both strengths). Coadministration of Celebrex with an aluminum and magnesium containing antacid resulted in a reduction in plasma celecoxib concentrations (Cmax: ↓ 37%; AUC: ↓ 10%).

Dose proportionality: Both AUC and Cmax are not dose proportional. The dose adjusted parameter values reduce with an increase in dose due to the poor solubility of the drug. However, the AUC is roughly dose proportional between the 100 mg and 200 mg doses. The deviation from dose proportionality is reduced under fed conditions.

Distribution: Celecoxib is highly plasma protein bound and the binding is linear within clinical dose range (~97%). In vitro studies indicate it binds to human plasma albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, suggesting extensive distribution into tissues.

Metabolism: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors in the in vitro models.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite with low amounts of the glucuronide also appearing in the urine. The low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The overall effective half-life, based on a single dose of celecoxib, is approximately 11 hours. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special populations

Effects of age, gender and race: At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax (1363 vs. 973 ng/mL) and a 70% higher AUC compared to the young subjects. In elderly females celecoxib Cmax and AUC are higher than those for elderly males but these increases are thought to be due to lower body weight in elderly females. There are no studies conducted in pediatric subpopulation.

Effects of gender: A meta analysis did not show any difference in celecoxib AUC between genders. A (14%) lower Cmax in female subjects was found to be statistically significant after a single dose of celecoxib. On the other hand, there was no difference in Cmax between genders after multiple dosing. Therefore, there is no consistent evidence of gender differences in celecoxib pharmacokinetics.

Effects of race: A meta analysis of pharmacokinetic studies suggested a (30%) higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this difference is unknown.

Hepatic insufficiency: A pharmacokinetic study showed that steady state celecoxib AUC increased (~30%) in volunteers with mild hepatic impairment (Child-Pugh Class I) and more than doubled (270%) in volunteers with moderate hepatic impairment (Child-Pugh Class II) when compared to the matching control group. Patients with severe hepatic impairment have not been studied.

Renal insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic moderate renal insufficiency (GFR) than that seen in subjects with normal renal function. No significant relationship was found between serum creatinine or estimated creatinine clearance and celecoxib clearance. Further, patients with severe renal insufficiency have not been studied.

Drug interactions

In vitro studies: In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4. Although not a substrate, in vitro studies indicate that celecoxib is a moderately potent inhibitor of cytochrome P450 2D6. (The Ki value for inhibition of bufuralol 1'-hydroxylation was ~4.2 μM, which is approximately 10-fold weaker than quinidine.) This finding suggests that there is a potential for an in vivo drug interaction with CYP2D6 substrate.

In vivo studies:
Glyburide, ketoconazole, phenytoin and tolbutamide: The effect of celecoxib on the pharmacokinetics of these drugs has been studied in vivo and clinically important interactions have not been found.

Fluconazole: Concomitant administration of fluconazole resulted in an increase of 68% in Cmax and 134% in AUC. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with Celebrex 200 mg BID as compared to subjects receiving lithium alone, which is similar to previous findings with other NSAIDs.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, Celebrex did not have significant effect on the pharmacokinetics of methotrexate.

Warfarin: The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time.

Bioequivalence of commercial formulations:
The sponsor has shown bioequivalence between the 100 mg and 200 mg commercial capsules. The 100 mg capsules are bioequivalent to the 100 mg Phase III capsules in terms of AUC but the Cmax is lower for the commercial capsules. A study was conducted to demonstrate the bioequivalence of the 200 mg commercial capsules to the 200 mg Phase III capsules. Because of the design and analysis method used, this study is currently evaluated by Dr. Shan Sun of QMRS/FDA.

II. Recommendation

The sponsor has adequately characterized the pharmacokinetics and pharmacodynamics of the subject drug. From the biopharmaceutic standpoint, the application is approvable provided that the sponsor addresses the issues as listed under "Comments to be Conveyed to the Sponsor."

III. Comments

A. General Comments:

1. Celecoxib has two important characteristics: (a) low aqueous solubility and high permeability, and (b) extensively metabolized in the liver which is predominantly mediated via CYP2C9; elimination through renal excretion of the parent compound is negligible.
2. The low aqueous solubility of celecoxib contributed to the high variability in absorption after oral administration.
3. In patients with chronic moderate renal insufficiency (GFR , the apparent clearance (CL/F) appears higher resulting in a 40% lower AUC when compared to studies in healthy subjects. This may be due to an increase in the unbound drug in renal impairment patients. However, this study is still under review as the individual report was not provided to this reviewer in the original submission.
4. A population PK analysis in OA and RA patients has been performed by the sponsor to characterize celecoxib pharmacokinetics in these patients and to identify possible covariates. However, due to the inappropriate study design, the analysis is deemed unreliable.
5. A population PK/PD analysis of four dental pain trials was included in the original submission. After receiving comments from this reviewer, the sponsor submitted a revised analysis which is currently under review.

B. Comments to be Communicated to the Sponsor:

1. It seems that low solubility prolonged absorption process making the terminal half-life appear longer than the true half-life of the drug. This is based on the much shorter terminal half-life seen in subjects taking the drug immediately after a high fat meal. It

follows that the amount of water taken by a subject may also affect the absorption and apparent terminal half-life of the drug. The sponsor should comment on this.

2. Very high plasma celecoxib concentrations were observed in 6 out of several hundred subjects exposed to the 200 mg dose. These may be poor metabolizers but more information is needed from the sponsor. These subjects were on single dose or short term multiple dose use of celecoxib and no serious adverse events occurred during the study. However, Dr. Maria Villalba, Medical Offier of HFD-550, indicated that many lab tests were performed several days after the last dose.

3. We have requested the following information but have not received a response from the sponsor:
   a. Effective half-life of the drug
   b. Volume of distribution at steady state
   c. Genotyping information for subjects with very high plasma celecoxib concentrations.

4. Regarding study 004: Values for CL/F and V_z/F in the individual report (Vol. 1.85, pp. 43, 47) differ from those in the summary (Vol. 1.81, p. 166). Discrepancies were also observed with Study 003. The sponsor should clarify.

APPEARS THIS WAY
ON ORIGINAL

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. _____
FT Initialed by Dennis Bashaw, Pharm.D. _____

CPB Briefing (Date: 11/24/98; Attendees: and Lee)

CC:
NDA 20-998
HFD-550 (Div.File)
HFD-550 (CSO/Lutwak)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

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IV. Background

Celecoxib (SC-58635), is a specific COX-2 inhibitor intended for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and management of pain. Cyclooxygenase (COX) is present in at least two forms in human cells. One form is constitutive (COX-1) and is widely expressed in nearly all tissues throughout the body, including gastric and renal epithelial cells, and platelets. The other form (COX-2) is inducible and is generally expressed in very low amounts in normal tissues, but is prominently expressed in inflamed tissues. Currently available NSAIDs are considered non-specific COX inhibitors. The sponsor claims that celecoxib inhibits COX-2 approximately 300-fold more effectively than COX-1 in in vitro studies. It is thought that COX-2 specific inhibitors will provide efficacy as an antiinflammatory and analgesic agent while minimizes adverse events associated with COX-1 inhibition (gastrointestinal ulceration, platelet dysfunction and nephrotoxicity).

Celecoxib has an aqueous solubility of about 5 μg/mL at between 5 and 40°C, which is pH independent below pH 9. It is freely soluble in methanol, ethanol, PEG 400 and acetone and very slightly soluble to practically insoluble in oils (< 3 mg/mL in corn oil) and non-polar hydrocarbons. Its pK_a of 11.1 is associated with ionization of the sulfonamide moiety. The apparent octanol/water partition coefficient for celecoxib is above 10^3 at pH 7. Therefore, it is a low solubility, high permeability drug.

V. Formulation

The sponsor intends to market both the 100 mg (blue) and 200 mg (gold) capsules. As shown in the table below, the formulations for these two strengths are not proportionally similar.

Ingredient	mg/Capsule		Function
	100 mg Capsules	200 mg Capsules	
Lactose, Monohydrate			
Sodium Lauryl Sulfate			
Povidone			
Croscarmellose Sodium			
Magnesium Stearate			

VI. Analytical Methods

VII. Summary of Bio/PK/PD Characteristics

(Note: For easy reference, the study number cited in this section corresponds to the last three digits of protocol numbers given in Appendix 1.)

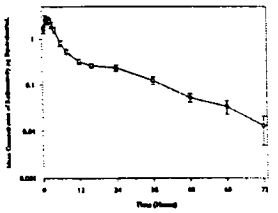
METABOLISM

a. Evaluation of Total Radioactivity in Human Biological Samples (Study 006)

This study was conducted (1) to determine the ADME profile (mass balance) of an oral fine suspension of celecoxib and (2) to estimate the bioavailability of an oral capsule relative to the fine suspension. Each subject received a single 300-mg dose of suspension and capsule (containing cold drug) formulations. The detailed study design is given in Appendix 1 (p. 62). This section discusses the results from the suspension formulation as related to the first objective.

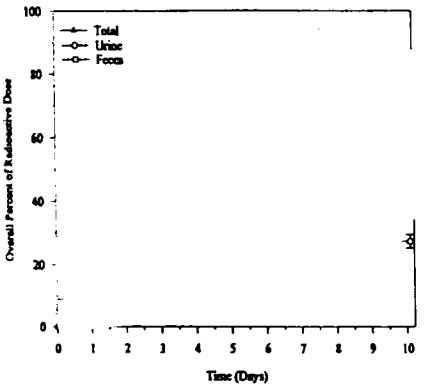
Eight healthy male subjects (2 in pilot phase and 6 in definitive phase) completed the study. Concentrations of total radioactivity in plasma, red blood cells, saliva, urine, and fecal samples collected at specified time intervals after dose administration were determined.

Plasma concentration of total Radioactivity: The mean plasma concentration of total radioactivity reached a maximum of 2.75±1.29 μg equivalents/mL at 1.75 hr postdose. Radioactivity in plasma obtained 72 hours after dose administration was not detectable in most subjects. The elimination half-life of total radioactivity was approximately 17.0±4.0 hrs.



Distribution into red blood cells: Celecoxib concentrations in plasma and RBC were compared at 1 and 4 hours postdose. The mean concentration of radioactivity was slightly lower in red blood cells than in plasma at 1 and 4 hours postdose (RBC: 2.33±0.34 and 1.26±0.22 μg/mL; plasma: 2.43± 0.49 and 1.57±0.17 μg/mL, respectively). The mean of individual ratios of RBC/plasma concentrations of total radioactivity were 1.02±0.3 and 0.80±0.29 at 1 and 4 hours postdose, respectively.

Excretion in urine and feces: Radioactivity was excreted in urine and feces following oral administration of celecoxib. The mean percent of total radioactivity excreted was 27.1±2.2% in the urine samples and 57.6±7.3% in fecal samples. As shown in the figure, most (95.6%) of the urinary excretion occurred within the first 24 hours postdose while ~78% of the fecal excretion occurred within 96 hours postdose.



Saliva: The concentration of radioactivity in saliva was very low at the time periods examined. Most of the saliva samples had no quantifiable concentrations of radioactivity. The amount of radioactivity secreted into the saliva up to 24 hours postdose was negligible.

Total recovery: Recovery from saliva and fecal wipes were very small (~0.14%). The total mean percent of the radioactive dose recovered (84.8±4.9%) were mostly from urine and feces.

Conclusion:

- Celecoxib was not preferentially bound to erythrocytes.
- Secretion of celecoxib into saliva was negligible.
- After oral administration of 300 mg celecoxib, approximately 85% of the dose was recovered from urine and feces (27.1±2.2% of the dose from urine and 57.6±7.3% of the dose from feces).

b. Metabolic Profiles in Biological Samples

Plasma: Plasma samples obtained at 0.5, 3, 4 and 12 hours after oral administration of celecoxib at 300 mg were analyzed using The findings were:

- The parent compound was the major species present in plasma. (*Reviewer's note*: In a drug interaction study with fluconazole, the AUC of M2 was found to be comparable to that of the parent compound when celecoxib was administered alone.)
- Three metabolites of celecoxib were found in plasma: SC–60613, SC–62807 and the glucuronide conjugate of SC–62807. Note: These metabolites were shown to be inactive as COX inhibitors in in vitro models.
- SC–60613 is the product of partial oxidation of the methyl moiety of celecoxib to a hydroxyl group and is a minor circulating metabolite as indicated in the table below.
- SC-62807 (M2) is the result of complete oxidation of the methyl moiety of celecoxib to a carboxyl group. Glucuronidation of the carboxyl metabolite forms M1. (See next page for chemical structures.)

Celecoxib and Metabolites in Plasma (in terms of % total radioactivity in plasma samples)

Time ,hr postdose		M1	M2	SC-60613	Celecoxib
0.5	(n=8)	1.10 ± 0.60	12.1 ± 2.6	2.43 ± 0.89	84.4 ±3.6
3	(n=8)	21.0 ± 4.9	21.2 ± 1.9	0.217 ± 0.182	57.6 ± 6.5
4	(n=2)	13.5	21.0	0.00	65.6
12	(n=6)	23.2 ± 4.1	27.0 ± 5.9	0.00 ± 0.0	49.9 ±4.5

Urine: Urine samples collected up to 12 hours postdose were analyzed

- No unchanged drug was detected in the urine.
- The species present in these samples were metabolites M1 and M2. The mean (n=8) cumulative amount of metabolites excreted in the urine within 12 hours postdose was equivalent to 18.8±2.1% of the dose for M2 and 1.48±0.15% of the dose for M1.

Feces: Analysis of fecal samples collected over 8-10 days after dosing gave the following results:

- The radioactivities in fecal samples were associated with metabolite M2 and the parent drug.
- The mean cumulative amount excreted in the feces were equivalent to 54.4 ± 6.8% (M2) and 2.56 ± 1.09% (celecoxib) of the dose, respectively.

Mean Percent of Dose Excreted In Urine and Feces

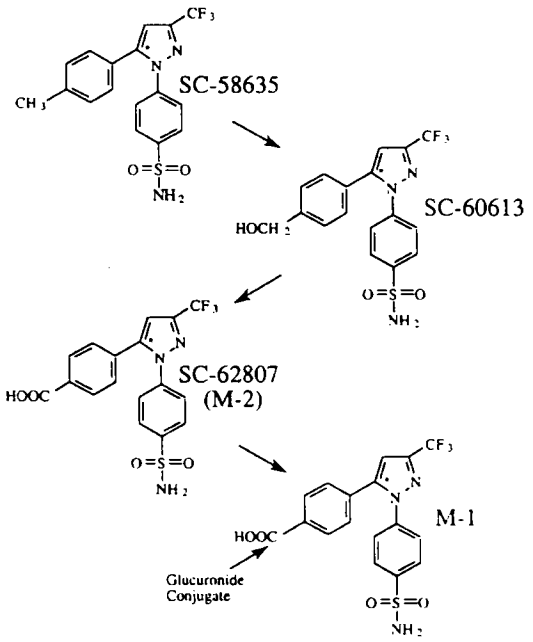
	Glucuronide of SC-62807 (M1)	SC-62807 (M2)	SC-60613	Celecoxib
Urine $_{(0\text{-}12\ hrs)}$	1.48 ± 0.15	18.8 ± 2.1	-	-
Feces	-	54.4 ± 6.8	-	2.56 ± 1.09

Conclusion:

- Urinary radioactivity was associated with M1 and M2. No unchanged drug was detected in the urine.
- Fecal radioactivity was associated with unchanged drug and M2.
- Metabolism of celecoxib was extensive. After oral administration, only approximately 2.56 ± 1.09% of the recovered total radioactivity in urine and feces was unchanged drug.

c. Proposed Metabolic Pathway

The sponsor proposed that celecoxib first undergoes partial oxidation of the methyl group to form a hydroxymethyl derivative (SC-60613), which was further oxidized to a carboxylic acid compound (SC-62807; M2). Glucuronidation of the carboxylic acid forms M1. (See figure below.)



Chemical structure and metabolic pathways of SC-58635. Asterisks indicate the position of the labeled carbon atoms.

d. In Vitro Studies: Determination of P450 Isoforms in the Metabolism of Celecoxib

The in vitro metabolism of -celecoxib was investigated using human liver microsomes and cDNA-expressed human cytochrome P450 enzymes. The major metabolites of celecoxib generated by human liver microsomes, SC-60613 and SC-62807, are the same as the major (unconjugated) metabolites found in vivo. The apparent K_m and V_{max} for celecoxib metabolism by a pool of human liver microsomes were estimated to be 49.3 μM (18.8 μg/mL) and 735 pmole/min/mg, respectively. The following studies were conducted using a protein concentration of 1.0 mg/mL.

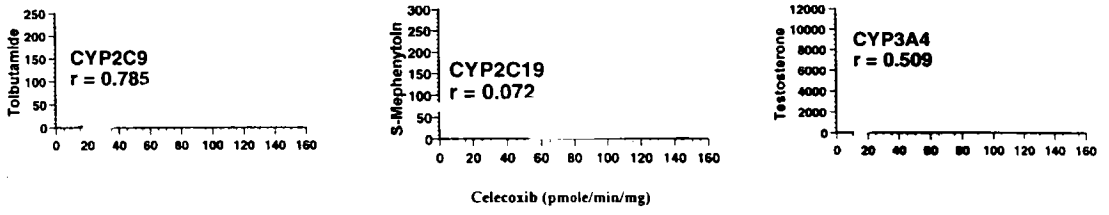
Celecoxib metabolism by cDNA-expressed human P450 enzymes: As shown in the table below, human recombinant CYP2C9, CYP2C19 and CYP3A4 were each found to be capable of metabolizing celecoxib to SC-60613 in vitro. Metabolism of -celecoxib was not detectable with human recombinant CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 and CYP3A5.

Table: Percent of Celecoxib Converted to SC-60613

1A2	2A6	2B6	2C9	2C19	2D6	2E1	3A4	3A5	PHM[1]
<0.5	<0.5	<0.5	38.7	64.4	<0.5	<0.5	2.1	<0.5	48.2

[1]Pooled human liver microsomes

Correlation of celecoxib metabolism with metabolism of P450 isoform-specific substrates by human liver microsomes: Specific enzymatic activities for -celecoxib metabolism at the celecoxib substrate concentrations of 2.6 and 10 μM (~1.0 and 3.81 μg/mL) were determined for 16 individual human microsome samples and compared to the known (phenotyped) specific enzymatic activities of the same microsomes for a series of cytochrome P450 isoform-specific substrates. The figures below present the correlation between isoform specific substrate metabolism and celecoxib metabolism at 2.6 μM celecoxib substrate concentration. Celecoxib metabolism correlated strongly with CYP2C9 (tolbutamide hydroxylase; $p < 0.001$). The correlation was weaker for CYP3A4 (testosterone 6β-hydroxylase; $p < 0.05$), and there was no correlation for CYP2C19 (S-mephenytoin 4'-hydroxylase). Similar results were obtained at the higher celecoxib substrate concentration (10 μM).



Inhibition of celecoxib metabolism by known cytochrome P450 inhibitors: The experiments with known inhibitors of P450 were performed at a celecoxib substrate concentration of 10 μg/mL and inhibitor concentrations of 20 μM furafylline, sulfaphenazole, omeprazole, 20 μM mephenytoin, 20 μM quinidine, 20 μM DDTC, 20 - 100 μM TAO or 0.5 - 1.0 μM ketoconazole.

Further evidence for the importance of CYP2C9 in celecoxib metabolism by human liver microsomes was provided by the finding that sulfaphenazole, a potent and specific CYP2C9 inhibitor, inhibited both celecoxib and tolbutamide to the same extent in six individual human microsome samples. Other cytochrome P450 isoform selective inhibitors were less effective (omeprazole/CYP2C19; troleandomycin/CYP3A4; ketoconazole/CYP3A4), or ineffective (furafylline/CYP1A; quinidine/CYP2D6; DDTC/CYP2E1) as inhibitors of ^{14}C-celecoxib metabolism by human liver microsomes.

Table: Percent Inhibition of Celecoxib Metabolism by Various Inhibitors

1A	2C9	2C19	2C19	2D6	2E1	3A4	3A4
furafylline	sulfa-phenazole	omeprazole	mepheny-toin	quini-dine	DDTC	TAO	ketoconazole
10.0	80.0	57.3	4.3	0	0	0	-
-	70.4 (10μM)	27.5 (10μM)	-	-	-	14.7 (100 μM)	36.9 (1.0 μM)

*Inhibitor concentration at 20 μM unless otherwise specified.

Conclusion:

- Human recombinant CYP2C9, CYP3A4 and CYP2C19 were each found to be capable of metabolizing celecoxib.
- CYP2C9 is judged to be most important in human metabolism of celecoxib based on correlation analysis using a series of characterized human microsome samples (high correlation found between celecoxib and tolbutamide metabolism) and the strong inhibition of celecoxib metabolism by the specific CYP2C9 inhibitor, sulfaphenazole.

Reviewer's comment:

All the above in vitro metabolism studies were performed at a high celecoxib concentration (10 μg/mL) except for the correlation study which used a celecoxib concentration (1 μg/mL) within the range found at the recommended dose (steady state Cmax: < 2 μg/mL after 200 mg BID).

PROTEIN BINDING

a. Report MRC-94S-0136

- In an in vitro protein binding study using plasma sample from one subject and employing a dextran–coated charcoal method, celecoxib was found to be highly protein bound at celecoxib concentrations of 0.3 μg/mL (97.3% bound) and 3.0 μg/mL (90.6% bound), respectively.

b. The Binding of SC-58635 to Mouse, Rat, Dog and Human Plasma Proteins

(Report # M3097065)

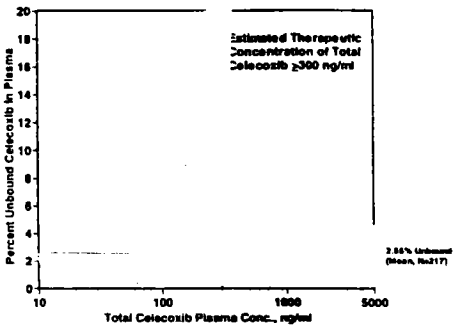
An ultracentrifugation method was employed in this study. celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μg/mL were evaluated. Only the results related to human plasma protein binding is summarized here. (Note: The human plasma was obtained from only one subject.)

- The percentages of binding of celecoxib to human plasma in vitro at total celecoxib plasma concentrations of 0.1, 0.3, 1.0, 3.0 and 10.0 μg/ml were 98.2%, 97.9%, 96.5%, 96.7% and 96.3%, respectively.
- Celecoxib binds in vitro to both human albumin and α_1-acid glycoprotein.
- The percentages of binding of celecoxib to human albumin in vitro at celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μg/mL were 100, 100, 99.8, 99.9 and 99.8, respectively.
- The percentages of binding of celecoxib to human α_1-acid glycoprotein in vitro at celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μg/mL were 92.4, 91.6, 91.0, 88.4 and 78.6, respectively.

c. Study 032

This study was conducted to evaluate the effects of 600 mg celecoxib BID versus 500 mg naproxen BID on platelet function in normal healthy subjects. Eight volunteers (3 male, 5 female,) received a single oral dose of celecoxib 600 mg with food, followed by celecoxib 600 mg BID with food for seven days. Blood samples for total and unbound celecoxib plasma assays were collected for up to 48 hours after single dose and last BID dose, in addition to trough plasma samples on predetermined days.

The dose of celecoxib in this study was higher than the anticipated therapeutic dose for treatment of osteoarthritis or rheumatoid arthritis. Total celecoxib plasma concentrations ranged from and unbound concentrations ranged As shown in the figure, the fraction of unbound drug remained rather constant (mean 2.55% unbound). Therefore, within the projected plasma concentration range for the clinical doses, total celecoxib plasma concentrations were considered an adequate measure for determination of celecoxib pharmacokinetics.



Conclusion:
Celecoxib is highly plasma protein bound (~97%). The fraction of unbound drug remained essentially constant (mean 2.55% unbound) at total plasma celecoxib concentrations

SINGLE DOSE PHARMACOKINETICS

Dose Escalation Study In Healthy Adult Volunteers (Study 001)

The objective of this exploratory study was to determine the safety, tolerability and pharmacokinetics of single, oral escalating doses of celecoxib administered to healthy male subjects. A total of 80 subjects participated and completed the fasting portion of the study. Six of the eight subjects who received the 200 and 400 mg doses under fasting conditions also received a single dose following a high fat breakfast. The detailed study design is given in Appendix 1 (p. 65).

Plasma data: The mean pharmacokinetic parameters for the doses ranging are listed below. Under fasting conditions, C_{max} was achieved within 2 hours for all of the doses tested. The sponsor considered that AUC_{0-96} was dose proportional through the 600 mg dose and less than proportional at the 900-mg and 1200-mg doses. The plasma terminal half-life, $T_{1/2}$, ranged from for the doses of 50-900 mg.

Food delayed peak plasma levels but increased the overall absorption of celecoxib (AUC ↑22% for the 200 mg dose and ↑58% for the 400 mg dose), suggesting a possible food effect.

Table: Mean (±SD) Parameter Values

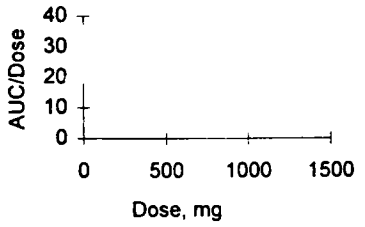
SC-58635 Dose	AUC(0-96) ng*hr/ml	Cmax ng/ml	Tmax hr	T1/2 hr
5 mg (n=4)	171.98 (40.85)	27.98 (9.71)	1.63 (1.11)	4.51 (0.78)
25 mg (n=4)	792.66 (249.30)	133.25 (45.18)	1.25 (0.50)	10.34 3.84)
50 mg (n=4)	1271.48 (307.92)	233.25 (45.07)	2.00 (1.15)	7.69 2.66)
100 mg (n=4)	2465.42 (690.41)	362.00 (155.98)	1.38 (0.75)	8.53 (2.89)
200 mg (n=4)	6271.63 (2846.27)	797.00 (498.78)	1.75 (1.50)	7.57 (5.47)
200 mg*(n=4)	7830.30 (4265.31)	875.50 (749.49)	6.25 (4.03)	9.51 (5.64)
400 mg (n=4)	7417.91 (904.52)	706.75 (104.08)	2.25 (1.50)	7.46 (2.38)
400 mg*(n=2)	11884.16 (3158.40)	1355.00 (7.07)	6.00 (2.83)	4.22 (2.31)
600 mg (n=4)	15725.65 (6689.83)	1771.00 (625.05)	1.50 (1.00)	9.56 (3.72)
900 mg (n=20)	18028.26 (7517.36)	1419.25 (683.38)	1.90 (0.91)	10.92 (5.15)
1200 mg (n=4)	19135.97 (4654.86)	2022.50 (751.99)	2.00 (0.82)	16.39 (17.28)

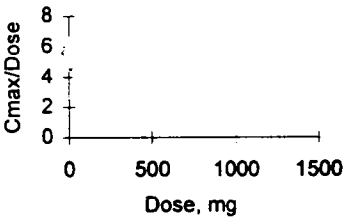
*Fed conditions

Reviewer's comments:

1. This study used a Phase 1 formulation which is different from the to-be-marketed formulation.
2. The sponsor considers that AUC was dose proportional up to 600 mg and less than proportional at 900 mg and above. This information is included in their proposed labeling.

As shown in the figures below, plots of dose adjusted AUC and Cmax versus dose indicate that there is a downward trend even for doses up to 600 mg for both AUC and Cmax, but the deviation from proportionality is greater for Cmax. The less than proportional increase in AUC is likely to be a result of less absorption due to the low solubility of the drug.





3. The long terminal half-life observed at the 1200 mg dose might be a complication of the absorption process since this is a low solubility drug.
4. The individual PK parameter values are not provided.

MULTIPLE DOSE PHARMACOKINETICS

a. Multiple-Dose Tolerability and PK Study In Healthy Subjects (Study 004)

This study was designed to determine the safety, tolerability and pharmacokinetics of SC-58635 after multiple dose administration in healthy subjects Doses of 40 mg, 200 mg and 400 mg or placebo were administered under fasting conditions as single doses, followed 48 hours later by BID dosing for 7 days. A total of 36 subjects completed the study with 24 subjects on active treatments. The detailed study design is given in Appendix 1 (p. 68).

Plasma data: Steady state plasma levels, as observed through trough plasma concentrations, were achieved within five days of BID dosing. The mean pharmacokinetic parameters following single and multiple dosing are tabulated below.

Mean (±SD) Parameter Values

Dose	AUC[a] ng*hr/ml	Cmax ng/ml	Tmax hr	T1/2 hr	CL/F L/hr/70 kg	V_z/F L/70 kg
Single Dose Phase						
40 mg (n=8)	1217 (±328)	197 (±86)	1.50 (±0.46)	4.18 (±1.95)	34.3 (±9.6)	194 (±81.5)
200 mg (n=7)	5986 (±4032)	646 (±341)	1.64 (±0.69)	8.01 (±2.33)	40.1 (±14.4)	483 (±260)
400 mg (n=8)	13341 (±3010)	1433 (±523)	2.13 (±0.79)	8.87 (±3.57)	31.4 (±6.9)	408 (±208)
Multiple Dose Phase						
40 mg (n=8)	937 (±288)	183 (±52)	1.94 (±0.90)	3.94 (±1.55)	45.1 (±14.4)	239 (±98)

200 mg (n=8)	6726 (±3858)	1115 (±425)	1.75 (±0.71)	7.09 (±2.33)	33.9 (±10.8)	346 (±176)
400 mg (n=8)	11634 (±3745)	1833 (±478)	1.63 (±0.99)	9.57 (±4.16)	38.2 (±13.8)	557 (±407)

(a) $AUC_{0-\infty}$ for single-dose phase and AUC_{0-12} for multiple-dose phase

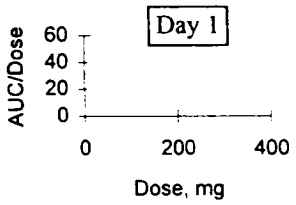
The single dose pharmacokinetics were generally predictive of those during multiple dosing (i.e., linear PK) as demonstrated by mean ratios of steady-state $AUC_{(0-12)}$ to single-dose $AUC_{(0-\infty)}$ of 79.3%, 118.7% and 84.8% for 40 mg BID, 200 mg BID and 400 mg BID doses, respectively. The terminal half-life was between 7 and 10 hours for the 200 mg and 400 mg doses. The accumulation ratios and %fluctuation as calculated from this study are presented below.

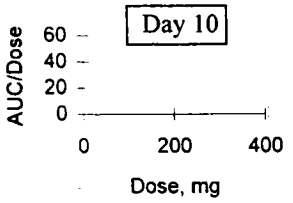
Table: Linearity, % Fluctuation and Accumulation Ratios

Dose	$AUC_{0-12(Day\ 10)}$ / $AUC_{inf(Day\ 1)}$ (%)	% Fluctuation	Accumulation Ratio[1]	Accumulation Ratio[2]
40 mg	79.3	205.6 (83.4)	1.03	1.88
200 mg	118.7	162.7 (67.1)	1.88	1.77
400 mg	84.8	114.1 (68.9)	1.42	1.19

% Fluctuation = (Cmax-Cmin)/(AUC_{0-12}/12) x 100 (Given as mean ±SD)
Accumulation Ratio[1] = $AUC_{0-12(Day\ 10)}$/ $AUC_{0-12(Day\ 1)}$ (Both mean and 90% CI are given)
Accumulation Ratio[2] = $Cmax_{0-12(Day\ 10)}$/ $Cmax_{0-12(Day\ 1)}$ (Both mean and 90% CI are given)

As shown in the figures below, the AUCs on both Day 1 (single dose) and Day 10 (steady state) appeared dose proportional across the dose groups. The apparent volume of distribution at terminal phase (V_z/F) was much greater than total body water (42 L/70 kg), suggesting extensive distribution of celecoxib in humans.





Reviewer's comments:

1. Tables of individual PK parameter values should be provided.
2. Values for CL/F and V_z/F in the individual report (Vol. 1.85, pp. 43, 47) differ from those in the summary (Vol. 1.81, p. 166). The sponsor should clarify.

b. Multiple-Dose Study In Older Subjects (Healthy Volunteers and OA Patients) (Study 003)

This study was conducted to investigate the safety, tolerability and pharmacokinetics in an older population Ten out of 36 subjects were osteoarthritis patients. A single dose of 40, 200, 400 or placebo was given to subjects under fast conditions followed 48 hours later by BID dosing for 14 days. The detailed study design is given on page 69. Note that smoking and caffeine consumption were allowed in this study.

Plasma data: The pharmacokinetic parameters are tabulated below. The peak plasma concentrations were reached within and half-life ranged Steady state plasma levels were achieved within 5 days of BID dosing as observed through the trough plasma concentrations.

Mean (±SD) Parameter Values

Dose	AUC (a) ng*hr/mL	Cmax ng/mL	Tmax hr	T1/2 hr	CL/F L/hr	Vd/F L
Single Dose						
40 mg	1928 ± 568	277 ± 77	3.4 ± 3.5	7.7 ± 2.9	22.6 ± 7.5	244 ± 107
200 mg	9941 ± 4488	759 ± 374	2.5 ± 1.7	15.2 ± 7.6	25.1 ± 15.2	467 ± 196
400 mg	14064 ± 5428	1103 ± 309	1.9 ± 0.7	14.5 ± 5.7	32.7 ± 13.6	649 ± 269
Multiple Dose						
40 mg	1687 ± 601	326 ± 119	1.7 ± 0.6	7.4 ± 1.7	26.2± 8.4	270 ± 78
200 mg	8155 ± 2427	1187 ± 393	2.1 ± 1.0	12.1 ± 3.7	26.2 ± 6.6	465 ± 205
400 mg	13355 ± 6599	1805 ± 642	3.8 ± 3.6	14.2 ± 4.5	36.4 ± 15.7	796 ± 517

(a) $AUC_{0-\infty}$ for single dose and AUC_{0-12} for multiple dose

The single dose pharmacokinetics observed in the study was generally predictive of that during multiple dosing as evidenced by the ratios of $AUC_{0-12(Day\ 10)}/AUC_{inf(Day\ 1)}$ (0.86) and no unexpected accumulation occurred as indicated by the ratio of $AUC_{0-12(Day\ 10)}/AUC_{0-12(Day\ 1)}$ (~2.0).

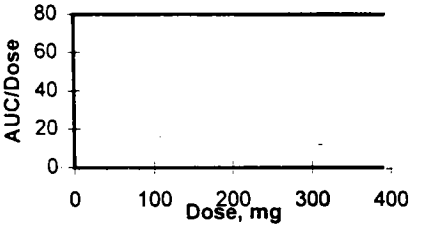
Dose	% Fluctuation	Accumulation Ratio[1]	Accumulation Ratio[2]	$AUC_{0-12(Day\ 10)}$ / $AUC_{inf(Day\ 1)}$
40 mg	181 ± 94	1.26	1.17	0.86
200 mg	83 ± 69	2.03	1.7	0.86
400 mg	82 ± 58	2.25	1.62	0.86

% Fluctuation = (Cmax-Cmin)/(AUC_{0-12}/12) x 100 (Given as mean ±SD)

Accumulation Ratio[1] = $AUC_{0-12(Day\ 10)}/AUC_{0-12(Day\ 1)}$ (Both mean and 90% CI are given.)

Accumulation Ratio[2] = $Cmax_{0-12(Day\ 10)}/Cmax_{0-12(Day\ 1)}$ (Both mean and 90% CI are given.)

Across dose groups, the dose-adjusted AUC decreased somewhat with dose.



Ex-Vivo PGE_2 and TXB_2: Four hours following a single oral dose (Day 1), the TXB_2 induced ex-vivo was significantly lower in the 200 mg and 400 mg dose groups (see table below). Eight days following multiple dosing (Day 10), TXB_2 concentrations were significantly decreased only in the 400 mg dose group. PGE_2 values were statistically significantly lower in all three treatment groups following both single and multiple doses of SC-58635 ($p \leq 0.05$).

Dose	A Day 1*, 0 hr	B Day 1*, 4 hrs	B-A (p-value**)	C Day 10, 4 hrs	C-A (p-value**)
TXB_2 concentration (ng/mL)					
40 mg	23.1 ± 16.1	15.6 ± 17.7	-7.6 ± 11.4 (p = 0.109)	19.7 ± 13.0	-3.4 ± 7.8 (p = 0.461)
200 mg	23.0 ± 10.6	12.0 ± 5.2	-11.0 ± 9.0 (p = 0.016)	16.0 ± 7.5	-6.7 ± 9.8 (p = 0.156)
400 mg	47.7 ± 43.1	25.9 ± 23.8	-21.8 ± 22.5 (p = 0.008)	22.5 ± 17.4	-25.2 ± 32.5 (p = 0.008)
PGE_2 concentration (pg/mL)					
40 mg	67.5 ± 35.3	47.4 ± 23.4	-20.1 ± 25.2 (0.023)	35.0 ± 19.6	-32.5 ± 21.2 (0.008)
200 mg	81.8 ± 40.5	33.5 ± 21.1	-48.3 ± 24.5 (0.008)	24.5 ± 21.1	-62.8 ± 31.9 (0.016)
400 mg	51.8 ±24.1	22.7 ± 13.1	-29.2 ± 13.6 (0.008)	15.7 ± 9.7	-36.1 ± 15.2 (0.008)

*Samples collected on Day 1 for the 40 mg & 200 mg dose groups and on Day 3 for the 400 mg group
**Based on the Wilcoxon signed rank test; n= 8 (40 mg & 400 mg dose groups); n=7 (200 mg dose group)

Reviewer's comments:

1. Reduction in induced PGE_2 on Day 10 was significant for all dose groups when compared to the "baseline value," but the magnitude of the decrease was not related to dose. Since the blood samples for ex-vivo TXB_2 and PGE_2 baseline were collected on different days for the 400 mg group (Day 1 for the 40 mg and 200 mg groups and Day 3 for the 400 mg dose group), this might have compromised the results.
2. The values of CL/F and V/F during the multiple dose phase in the individual report (Vol. 1.87, p. 43) are different from those in the summary (Vol. 1.81, p. 226). The sponsor should clarify.

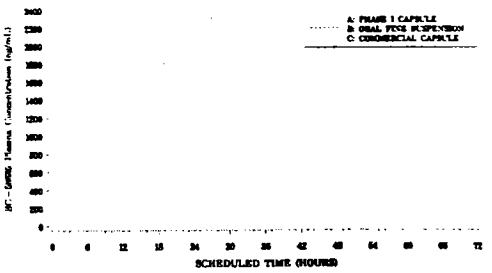
RELATIVE BIOAVAILABILITY

Commercial Capsule 200 mg and Phase I Capsules 100 mg vs. A Fine Suspension (Study 037)

The primary objective of this study was to determine the bioavailability of the Phase I celecoxib capsules (100 mg) and the commercial formulation capsules (200 mg) relative to an oral fine suspension. Thirty-six healthy subjects received each of the three treatments at a single dose of 200 mg on either Day 1, 8 or 15 according to a randomization schedule. Blood and urine samples were collected up to 72 hours postdose. The detailed study design is given in Appendix 1 (p. 83).

As shown in the figure below, there was a greater and more rapid early drug uptake in the oral fine suspension formulation compared to the Phase I and commercial capsules. However, by approximately 3 hours postdose, mean concentrations in the three formulations were comparable, with mean concentrations in the oral fine suspension group lowest after 3 hours (mean 72-hour levels were all below the assay sensitivity). It was evident that the oral fine suspension

formulation had higher C_{max} and shorter T_{max} compared to either the Phase I or commercial capsule formulations. The extent of absorption (AUC_{0-72}) from the two capsule formulations, however, was similar to the oral fine suspension formulation. The relative bioavailability for the commercial formulation was 99% relative to the suspension.



Urinary excretion of celecoxib was negligible (See tables below). The amount of metabolite M2 (SC-62807) excreted in the urine over 0-72 hours postdose was generally similar for the three formulations (of dose).

Table: Mean (%CV) Parameter Values and 90% CI for Ratios

Single-dose Celecoxib Pharmacokinetic Parameter	Treatment Mean (CV)[a]		Ratio: 200 mg Commercial Cap. / Suspension	90% Confidence Interval for Ratio[b]
	Commercial 1*200 mg Capsule (N=36)	Fine Suspension 200 mg (N=36)		
AUC(0-72) (hr·ng/ml)	7648 (32%)	7736 (32%)	99.0%	(94.6%, 103.5%)
AUC(0-∞) (hr·ng/ml)	7830 (31%)	8001 (32%)	-	-
C_{max} (ng/ml)	704.6 (38%)	1229 (37%)	57.8%	(51.1%, 65.4%)
T_{max} (hr)	2.83 (37%)	0.79 (41%)	-	-
Terminal T1/2 (hr)	11.9 (30%)	13.3 (50%)	-	-
CL/F (L/hr)[c]	27.7 (28%)	27.1 (28%)	-	-
SC-58635 XU(0-72) (% of dose)	0.001 (145%)	0.003 (122%)	-	-
SC-62807 XU(0-72) (% of dose)	22.3 (29%)	23.5 (24%)	-	-

Single-dose Celecoxib Pharmacokinetic Parameter	Treatment Mean (CV)[a]		Ratio: Suspension / 100 mg Phase I Cap.	90% Confidence Interval for Ratio[b]
	Fine Suspension 200 mg (N=36)	Phase I 2*100 mg Capsule (N=36)		
AUC(0-72) (hr·ng/ml)	7736 (32%)	7248 (33%)	107.3%	(102.5%, 112.2%)
AUC(0-∞) (hr·ng/ml)	8001 (32%)	7562 (33%)	-	-
C_{max} (ng/ml)	1229 (37%)	619.7 (40%)	197.0%	(174.2%, 222.9%)
T_{max} (hr)	0.79 (41%)	3.00 (33%)	-	-
Terminal T1/2 (hr)	13.3 (50%)	14.0 (38%)	-	-
CL/F (L/hr)[c]	27.1 (28%)	29.0 (31%)	-	-
SC-58635 XU(0-72) (% of dose)	0.003 (122%)	0.001 (222%)	-	-
SC-62807 XU(0-72) (% of dose)	23.5 (24%)	21.3 (31%)	-	-

DOSE PROPORTIONALITY OF COMMERCIAL CAPSULES

To demonstrate dose proportionality between celecoxib 100 mg and 200 mg commercial capsules, the sponsor combined data for 47 subjects who received one celecoxib 200 mg

commercial capsule in bioequivalence study 084 and data for 24 subjects who received one celecoxib 100 mg commercial capsule in food effect study 088. Only data for treatments given under fasted conditions were used (see table below). Individual celecoxib AUC and C_{max} values were doubled for the one 100 mg capsule treatment prior to assessment of dose proportionality by testing the significance of the difference between least square means of the two commercial capsule. From the p-values, the sponsor claimed the two commercial capsules are dose proportional.

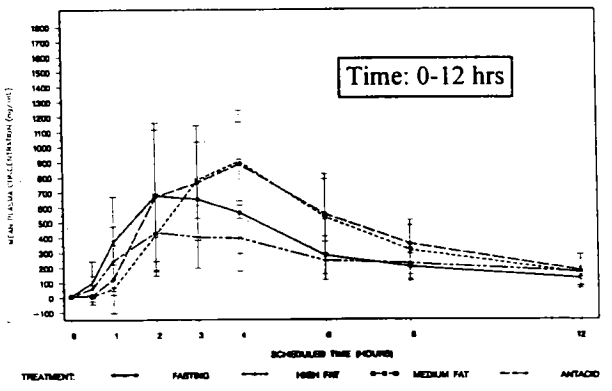
Single-dose Celecoxib Pharmacokinetic Parameter	Treatment Mean (CV) or Median (Range)		p-Value for Test of Difference Between Log LS Means[b]
	1*100 mg Commercial (N=24)	1*200 mg Commercial (N=47)	
AUC(0-lqc) (hr·ng/ml)	4416 (77%)	8063 (44%)	0.615
AUC(0-∞) (hr·ng/ml)	5127 (78%)	8829 (48%)	0.296
C_{max} (ng/ml)	455.0 (60%)	801.2 (46%)	0.501
T_{max} (hr)	2.6	2.5	NAV
Terminal T1/2 (hr)	16.0 (63%)	12.2 (52%)	0.310
C_{max}/AUC(0-lqc)	0.11 (36%)	0.10 (34%)	NAV

Reviewer's comment:
The validity of this approach is questionable since data from one particular study for each strength was chosen to fit the need. It is noted that there were other studies available but were not selected. For example, Study 019 (food effect study for the 200 mg commercial capsules) gave a mean AUC_{∞} of 6564 (±2383) ng.hr/mL following a single dose administration of the 200 mg commercial capsules under fasted conditions. It appears that using this study will fail the dose proportionality in AUC_{∞}. The sponsor should justify the selection of particular studies for the statistical test. (Additionally, p-values are given in the above table but not the power for detecting a 20% difference. In view of the high variability in parameter values, especially for the 100 mg capsules, this information is essential.) In our view, true dose proportionality between the commercial 100 mg and 200 mg capsules was not established

EFFECT OF FOOD AND ANTACID

a. 200 mg Celecoxib Commercial Capsules (Study 019)

The food effect on the bioavailability of celecoxib 200 mg capsules was assessed in 24 healthy subjects after administration of a single 200-mg dose. Both high-fat and medium-fat meals were examined. In addition, the effect of antacid was also investigated. Detailed study design is given on page 70. The plasma concentration-time profiles (0-12 hrs postdose) are shown in the figure.



High fat meal vs. fast:
Compared to the fast conditions, administration of 200 mg celecoxib with high fat (75 g) meal resulted in a slower rate of absorption (Tmax: increased from 2.4 to 3.4 hrs) and a greater extent of absorption (AUC_{0-48}: ↑22%; AUC_{∞}: ↑11%; Cmax: ↑39%).

Medium fat vs. fast: Following administration of 200 mg celecoxib with medium fat (8 g) meal, Tmax increased to 3.7 hrs, but both the AUC and Cmax increased to a less degree (AUC_{0-48}: ↑12%; AUC_{∞}: ↑1%; Cmax: ↑31%).

Antacid: Coadministration of antacid to fasted subjects reduced both the rate and extent of absorption of celecoxib (AUC_{0-48}: ↓6%; AUC_{∞}: ↓10%; Cmax: ↓37%) although Tmax was largely unaffected.

Table 1: Arithmetic Mean (±SD) Parameter Values

Fast/Fed/Antacid	AUC_{0-48} ng.hr/mL	AUC_{∞} ng.hr/mL	Cmax ng/mL	Tmax hr	T1/2 hr
Fast	5884 ± 2293	6564 ± 2383	806 ± 411	2.4 ± 0.8	14.1 ±11.4
High-Fat Meal	7141 ± 2787	7318 ± 2818	1042 ± 355	3.4 ± 1.3	6.3 ± 2.8
Medium-Fat Meal	6607 ± 2719	6894 ± 2832	952 ± 244	3.7 ± 0.8	6.2 ± 2.5
Fast/Antacid	5729 ± 2628	6116 ± 2712	507 ± 259	2.5 ± 1.1	10.6 ± 3.1

Table 2: Ratio of parameter values and the corresponding 90% confidence intervals

Comparison	AUC_{0-48} ng.hr/mL	AUC_{∞} ng.hr/mL	Cmax ng/mL
High fat meal vs. Fast	122.3% (112.0 - 133.5%)	110.7% (100.2 - 122.3%)	139.2 (113.4 - 170.9)
Medium fat meal vs. Fast	111.6% (102.2 - 121.9%)	100.8 (91.1 - 111.5)	131.3 (107.0 - 161.2)
Fast + Antacid vs. Fast	94.5% (86.5 - 103.2)	89.7% (81.2 - 99.1)	62.7% (51.1 - 77.0%)

Conclusions:

- Administration of celecoxib 200 mg with high (75 g) and medium (8 g) fat content meals in the morning resulted in a slower rate of absorption (Tmax at 4 hours) with an increase in Cmax (~30% for medium fat meal; ~40% for high fat meal) and AUC relative to administration in the fasting state.
- Administration of celecoxib 200 mg with antacid, given under a fasting state, resulted in a similar Tmax (~ 2.5 hours) with a decrease in Cmax (37%) and AUC (~ 10%) relative to dosing under the fasting state.

b. 100 mg Commercial Capsules (Study 088)

This study examined the food effect on the bioavailability of 50 and 100 mg capsules after a single dose administration in 24 healthy subjects. Since the sponsor does not intend to market the 50 mg capsules, the focus will be on the 100 mg capsules. The detailed study design is shown on page 76.

Under fast conditions, Cmax was reached within 2-3 hours after dosing. Food delayed but increased the extent of absorption. As shown in the table below, mean Tmax increased to hours and mean AUC_{∞} increased approximately 10% for both strengths when the dosage forms were taken immediately following a high-fat breakfast.

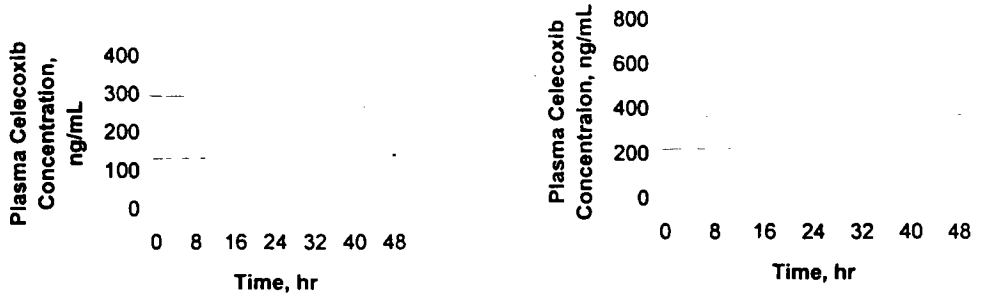


Table 1: Arithmetic Mean ±SD (%CV) Parameter Values

Parameter	50 mg/Fast		50 mg/fed		100 mg/fast		100 mg/fed	
AUC_{0-48} (ng.hr/mL)	2426 ± 2183	(90.0)	2601 ± 1873	(72.0)	4463 ± 3387	(75.9)	5215 ± 3313	(63.5)
AUC_{∞} (ng.hr/mL)	2694 ± 2592	(96.2)	2759 ± 2281	(82.7)	5127 ± 4020	(78.4)	5419 ± 3890	(71.8)
Cmax (ng/mL)	321 ± 178	(55.5)	354 ± 130	(36.6)	455 ± 275	(60.5)	747 ± 382	(51.1)
Tmax (hr)	2.9 ± 1.6	(53.9)	4.5 ± 1.4	(30.3)	2.6 ± 1.2	(47.0)	5.0 ± 2.4	(47.9)
T1/2 (hr)	11.0 ± 6.7	(60.7)	6.5 ± 3.9	(60.2)	16.0 ± 10.2	(63.5)	6.9 ± 3.0	(44.5)

The ratios of least square means (high fat/fast) and the corresponding 95% CI for both AUC and Cmax are given in the table below. When taken with a high fat meal, the Cmax and AUC of the 100 mg capsules increased 62% and

Ratio of Least Square Means and 95% Confidence Interval

Parameter	Ratio of Least Square Means (95% CI)	
	50 mg Capsules	100 mg Capsules
AUC_{0-48}(fed)/ AUC_{0-48}(fast)	1.12	1.20
AUC_{∞}(fed)/ AUC_{∞}(fast)	1.07	1.07
Cmax (fed)/Cmax (fast)	1.15	1.62

Dose proportionality: Under fed conditions, both the AUC and Cmax were dose proportional for the 50 mg and 100 mg doses. Under fast conditions, the ratios of dose-adjusted parameter means (100 mg capsule/50 mg capsule) were 0.71, 0.92 and 0.95 for Cmax, AUC_{0-48} and AUC_{∞}, respectively.

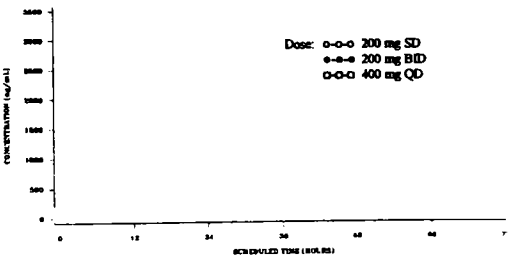
Comments:

1. The sponsor did not explain why a shorter T1/2 was observed under fed condition as compared to fast conditions. Since the drug has low aqueous solubility, the T1/2 observed under fast conditions might be complicated by the dissolution/absorption process.
2. The subjects in this study were primarily Hispanic/Latin American (75%). Large intersubject variability for Cmax and AUC were observed for both the 50 mg and 100 mg strengths.

DOSAGE REGIMEN: 200 mg BID vs. 400 mg QD (Study 043)

For better patient compliance, a treatment regimen of once-daily dosing is considered more desirable than twice-daily dosing. The primary objective of this study was to examine the feasibility of QD dosing. Twenty-four healthy subjects were given a single 200 mg dose followed 3 days later by a multiple dose phase in which subjects received 200 mg BID or 400 mg QD for 7 days and then were crossed-over to receive the alternate treatment. The detailed design is given on page 97.

Plasma data: The figure below shows the plasma concentration-time profiles for the single dose and multiple dose phases. For the 200 mg BID regimen, the morning trough levels were higher than the afternoon (12 hr after morning dose).



The mean pharamcokinetic parameter values are tabulated below. For the 200 mg BID treatment group, the PM dose yielded a 16% higher mean AUC than the AM dose. The accumulation ratio based on the AUC values was estimated to be 2.3 for the 200 mg AM dose and 2.0 for the 400 mg dose. The 400 mg QD regimen resulted in a 15% lower mean AUC_{0-24} and a 28% higher mean Cmax when compared to the 200 mg BID regimen (90% CI: 79.4-91.5% for AUC; 116.4-141% for Cmax). The sponsor considers the difference in bioavailability between the two regimens not clinically significant and that once a day dosing is possible.

Mean±SD (%CV) Pharamcokinetic Parameter Values

AUC (ng.mL/hr)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	Accumulation Ratio
Single Dose 200 mg				
0-12 hrs: 5654 ± 1789 0-24 hrs: 7597 ± 2470 •0-48 hrs: 8761 ± 3062 (35%)	1052 ± 324 (31%)	4.0 ± 1.2	8.8 ± 2.4	-
200 mg BID				
0-12 hrs • AM dose: 8281 ± 3230 (39%) • PM dose: 9601 ± 3264 (34%) 0-24 hrs: 17882 ± 6259	 1254 ± 414 (33%) 1256 ± 427 (34%) 1255 ± 406 (30%)	3.8 ± 0.5	7.3 ± 2.2	236%
400 mg QD				
•0-24 hr: 15615 ± 6090 (39%)	1760 ± 634 (36%)	4.6 ± 1.2	10.2 ± 2.8	202%

Urine data: Very small amount of the drug was excreted unchanged in the urine (≤0.02% of dose). Data for the metabolites were not provided.

Conclusions:

- At steady state, the 400 mg QD dosing resulted in a 15% lower mean AUC_{0-24} and a 28% higher mean Cmax when compared to the 200 mg BID regimen.

- After 200 mg BID dosing, the PM dose had higher AUC and trough levels than the AM dose. It is unclear whether this was due to interoccasional variability, circadian variation or simply food effect (different calorie content between evening and morning meals).

Comments:

1. The Tmax for the 200 mg BID regimen as listed by the sponsor is in error.
2. In the labeling, the sponsor is not explicitly proposing the use of a 400 mg dose but indicates that this dose has been studied.

Effect of Dosing Time: AM Dosing vs. PM Dosing (Study 069)

This study was designed primarily to compare the 400 mg QD AM dosing to 400 mg QD PM dosing in healthy subjects. Twenty-four subjects were given a single 400 mg dose on Day 1 followed 3 days later by a multiple dose phase in which subjects received 400 mg QD at 8AM or 7PM with low fat meal for 10 days and then were crossed-over to receive 400 mg QD at the alternate dosing time. The study design is given on page 92.

Plasma data:

Figure a: 0-72 hrs

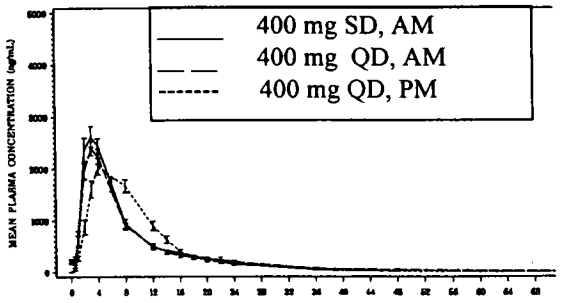
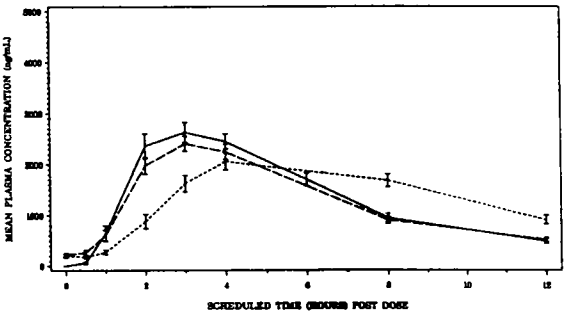


Figure b: 0-12 hrs



AM vs. PM Dosing: Compared to AM dosing, mean plasma concentrations following PM dosing tended to be lower during 0-5 hour postdose (with a longer Tmax), greater during postdose and then were similar between postdose. The mean ratios (PM/AM) were 1.09 (90% CI: 102.8-115.7%) for $AUC_{0\text{-}24hr}$ and 0.84 (90% CI: 75.6-94.2%) for Cmax. Cmin was lower for the PM dosing with a PM/AM ratio of ~0.75.

Table: Mean ± SD Parameter Values

Dosage Regimen	$AUC_{0\text{-}24hr}$ ng.hr/mL	Cmax ng/mL	Tmax hr	T1/2 hr
400 mg SD, AM	20208 ± 6621 22160 ± 7463*	2893 ± 930	3.1 ± 1.2	7.7 ± 2.4
400 mg QD, AM	18955 ± 6001	2565 ± 738	3.2 ± 0.6	10.1 ± 8.7
400 mg QD, PM	21034 ± 7703	2214 ± 758	4.5 ± 1.9	7.3 ± 2.8

* AUC_{∞}

The mean trough levels at the presumed steady state fluctuated appreciably on various days, suggesting high variabilities in the bioavailability of the drug.

Study Day	Mean Trough Levels, ng/mL	
	400 mg QD AM	400 mg QD, PM
Days 10-13		
Days 26-29		

Multiple vs. Single Dosing: Based on the observed AUC and Cmax values, no accumulation was found after 400 mg QD dosing when compared to a single dose administration.

Urine Data: Very small amount of the drug (~0.01% of the dose) was excreted unchanged in the urine. Approximately 40% of the dose was renally excreted as the metabolite SC-62807, the majority of which was excreted within the first 12 hours (See Figure). When compared to the PM dosing, the amount of SC-62807 excreted in the first 4 hours was substantially greater following AM dosing which is consistent with the observations of the plasma celecoxib concentrations.

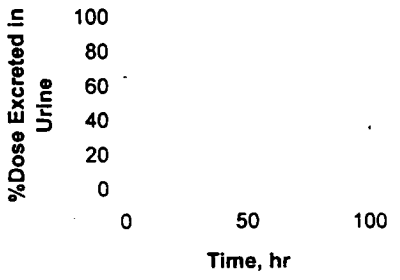


Table: Amount of SC-58635 and SC-62807 Excreted in Urine

Dosage Regimen	Study Day	Amount Excreted*, (μg)	
		SC-58635	SC-62807
400 mg SD, AM	Day 1	40.65 ± 26.55	145857 ± 36941
400 mg QD, AM	Day 13	42.3 ± 14.8	168684 ± 28817
	Day 29	50.7 ± 21.9	178095 ± 37116
400 mg QD, PM	Day 13	33.0 ± 17.7	166746 ± 44395
	Day 29	42.5 ± 15.6	162223 ± 32546

*0-48 hrs for Day 1 and 0-72 hrs for all other study days

Conclusion:

- With 400 mg QD regimen, PM dosing and AM dosing had comparable AUC values (PM/AM: 1.09) but PM dosing gave a longer Tmax and lower Cmax (PM/AM: 0.84) and Cmin (PM/AM: ~0.75).
- Approximately 40% of the dose was renally excreted as SC-62807 (M2) and only ~0.01% of the dose was excreted unchanged in the urine.

Comment:
In this study, PM dosing gave a lower Cmax and AUC while Study 043 suggested otherwise. The inconsistency in the results may be due to the large inter- and intra-subject variabilities.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Effect of Age: Healthy Young vs. Elderly Subjects (Study 015)

This study evaluated the pharmacokinetics of celecoxib in 24 healthy young (<50 years) and 24 healthy elderly (≥65 years) subjects. Each subject received a single oral dose of celecoxib

200 mg on Day 1, followed by celecoxib 200 mg BID dosing that began on Day 3 and ended after single morning dose on Day 10. (Additional 4 elderly and 4 young volunteers received single and BID doses of placebo.) Plasma and urine samples for celecoxib assay were collected at predetermined intervals for 48 hours after single dose and for 96 hours after last BID dose, respectively. The detailed study design is given in Appendix 1 (p. 102).

Pharmacokinetic results: Mean celecoxib plasma concentrations after multiple dosing (Day 10) in elderly subjects were those in young subjects. One elderly subject (no. 221, 73 year-old Caucasian female) had celecoxib plasma concentrations after both single dose and BID dosing that were substantially higher than any other subject in this study or any other study (Cmax: 2660 ng/mL on Day 1, and 10200 ng/mL on Day 10). The results summarized below include subject no. 221 except those for $AUC_{(0-\infty)}$ and terminal T1/2, which could not be estimated in this subject. At steady state, mean apparent clearance was 40% smaller and mean AUC_{0-12} and Cmax values were approximately 70% greater in the elderly than those in the young group. Mean T_{max} was comparable in both groups (2.41 hr vs. 2.72 hr) and the mean terminal T1/2 was slightly longer in the elderly group (12.4 vs. 11.3 hr).

As observed in previous studies, less than 0.1% of the dose was excreted unchanged in the urine. The amount of metabolite SC-62807 excreted renally was 18.6% of dose in the elderly group and 14.0% in the young group. (Reviewer's note: Previous studies showed urinary excretion of metabolite SC-62807 was about 20% of dose in healthy young volunteers.)

Celecoxib **Pharmacokinetic Parameter**	Treatment Group Mean (CV)[a] **Elderly (N=24)**	**Young (N=24)**	Ratio:[b] **Elderly / Young**	**95% Confidence Interval for Ratio[(b)]**
After Single Oral Dose of Celecoxib 200 mg (Day 1)				
$AUC_{(0-48)}$ (hr·ng/ml)	10385 (70%)	6270 (30%)	151.9%	(121.1%, 190.6%)*
$AUC_{(0-\infty)}$ (hr·ng/ml)	10143 (46%)[(c)]	6694 (30%)[(c)]	146.2%	(118.6%, 180.2%)*
C_{max} (ng/ml)	1019 (54%)	598.3 (54%)	176.3%	(131.2%, 236.8%)*
T_{max} (hr)	1.95 (39%)	3.42 (45%)	-	-
Terminal T1/2 (hr)	12.8 (34%)[(c)]	11.7 (39%)[(c)]	-	-
CL/F (L/hr/70 kg)	22.3 (30%)[(c)]	31.7 (34%)[(c)]	-	-
Vd/F (L/70 kg)	390 (30%)[(c)]	533 (51%)[(c)]	-	-
SC-62807 XU(0-48) (% of dose)	18.3 (45%)	15.6 (44%)	-	-
After Multiple BID Doses of Celecoxib 200 mg (Day 10)				
$AUC_{(0-12)}$ (hr·ng/ml)	11852 (113%)	5871 (35%)	172.0%	131.1 - 225.6 %*
$AUC_{(0-\infty)}$ (hr·ng/ml)	19446 (80%)[(c)]	9697 (38%)	185.2%	(144.3%, 237.6%)*
C_{max} (ng/ml)	1808 (104%)	973.2 (46%)	167.4%	(126.0%, 222.4%)*
$C_{min(0)}$ (ng/ml)	884.0 (154%)	391.4 (45%)	-	-
T_{max} (hr)	2.41 (43%)	2.72 (36%)	-	-
Terminal T1/2 (hr)	12.4 (21%)[(c)]	11.3 (33%)	-	-
CL/F (L/hr/70 kg)	23.7 (41%)	38.4 (46%)	-	-
Vd/F (L/70 kg)	448 (48%)[(c)]	630 (56%)	-	-
SC-58635 $XU_{(0-12)}$ (% of dose)	0.008 (205%)	0.006 (73%)	-	-
SC-62807 $XU_{(0-12)}$ (% of dose)	18.6 (38%)	14.0 (45%)	-	-

[a]Arithmetic mean [b]Ratio based on geometric means [c]N=23 [d]XU: Amount excreted in urine

- *Elderly females vs. young females:* There were statistically significant differences in steady-state celecoxib $AUC_{(0-12)}$, C_{max} and CL/F between elderly females and young females. In the elderly females, even after excluding subject 221, mean $AUC_{(0-12)}$ and C_{max} were approximately twice as high and CL/F was only half of the values observed in young females.
- *Elderly males vs. young males:* Mean Cmax and AUC were approximately greater in elderly males than in young males.

Multiple-dose Celecoxib PK Parameter	Treatment Group Mean (CV)[a]		Ratio[b]:	95% CI for Ratio
	Elderly Male (N=12)	Young Male (N=11)	Elderly Male / Young Male	
AUC(0-12) (hr·ng/ml)	8238 (32%)	6440 (33%)	130.5%	(98.6%, 172.8%)
C_{max} (ng/ml)	1254 (24%)	1089 (48%)	124.2%	(91.2%, 169.1%)
CL/F (L/hr)[d]	26.0 (24%)	35.1 (40%)	74.0%	(47.4%, 100.6%)
	Elderly Female (N=12)	Young Female (N=13)	Elderly Female/ Young Female	
AUC(0-12) (hr·ng/ml)	15466 (119%) 10309 (44%)[c]	5389 (35%)	223.3% 188.7%[c]	(142.0%, 351.2%) (136.9%, 260.1%)[c]
C_{max} (ng/ml)	2362 (109%) 1649 (44%)[c]	875.3 (41%)	221.8% 189.3%[c]	(139.4%, 353.0%) (132.2%, 271.1%)[c]
CL/F (L/hr)[d]	20.6 (46%) 22.3 (36%)[c]	42.0 (38%)	49.2% 53.1%[c]	(23.2%, 75.1%) (27.1%, 79.0%)[c]

[a]Arithmetic mean; [b]Ratio based on geometric means; [c]Subject #221 excluded.

Pharmacodynamic results: These data were reviewed by Dr. Maria Villalba, Medical Officer of HFD-550. The sponsor claimed the following:

- There were no statistically significant differences between elderly and young subjects in the mean changes of platelet aggregation induced by arachidonic acid or collagen. The mean change was greater for elderly females (-12.00±26.92) than for all elderly subjects (-5.58±20.73) though not statistically significant.
- There were statistically significant changes from pretreatment in platelet counts between elderly and young subjects at 8 hours postdose on Day 1 and at 8 hours postdose on Day 9, but these differences were not considered to be clinically significant because the magnitude of changes was greater for subjects receiving placebo.

Reviewer's comments:

1. Two subjects (elderly females; #221 & 222) in this study had unusually high plasma celecoxib concentrations. Subject #221 had the highest level among all studies. A genotype screening of v1 mutation indicated that these two subjects had the wild type 2C9 (i.e., not poor metabolizers). However, three v2 mutations were not screened.
2. Even when both Subjects #221 and 222 were excluded in the analysis, the mean (±SD) Cmax for elderly group was 1363±433 ng/mL, which was 40% higher than the young group. The mean value for AUC_{0-12} without these two subjects could not be calculated because individual data for AUC_{0-12} were not provided.

Gender Effect on Celecoxib Pharmacokinetics

Study 015: Based on the above study, the mean parameter values for males and females in the elderly and young groups in Study 015 are tabulated below.

PK Parameter	Treatment Group Mean (CV)[a]		Ratio[b]	95% CI for Ratio
	Young Female (N=13)	Young Male (N=11)	Young Female/ Young Male	
AUC(0-12) (hr·ng/ml)	5389 (35%)	6440 (33%)	83.5%	(61.0%, 114.2%)
C_{max} (ng/ml)	875 (41%)	1089 (48%)	81.6%	(55.8%, 119.4%)
CL/F (L/hr)[d]	42.0 (38%)	35.1 (40%)	119.4%	(83.0%, 155.8%)
	Elderly Female (N=12)	Elderly Male (N=12)	Elderly Female/ Elderly Male	
AUC(0-12) (hr·ng/ml)	15466 (119%) 10309 (44%)[c]	8238 (32%)	142.9% 120.7%[c]	(91.6%, 222.9%) (90.4%, 161.3%)[c]
C_{max} (ng/ml)	2362 (109%) 1649 (44%)[c]	1254 (24%)	145.8% 124.4%[c]	(95.5%, 222.4%) (94.1%, 164.5%)[c]
CL/F (L/hr)[d]	20.6 (46%) 22.3 (36%)[c]	26.0 (24%)	79.4% 85.6%[c]	(53.2%, 105.5%) (61.8%, 109.4%)[c]

[a]Arithmetic mean; [b]Ratio based on geometric means; [c]Subject #221 excluded.

- Elderly females vs. elderly males: When subject #221 was excluded from the analysis, mean celecoxib AUC and Cmax in elderly females was 20-25% higher than in elderly males (not statistically significantly different).
- Young females vs. young males: Mean celecoxib AUC and Cmax were approximately 20% lower in young females than in young males (not statistically significantly different).

Reviewer's comment:
Elderly females had higher Cmax and AUC than elderly males. The sponsor attributed this to body weight differences between the two groups without a formal analysis. It is noted that in this study the mean body weight in female subjects was about 20% lower than in male subjects.

Meta Analysis (Effects of Race and Gender)

Statistical analyses were performed on pooled data from Phase I studies to assess the effects of age, gender, body weight and race on celecoxib pharmacokinetics (270 subjects in 9 single dose studies; 112 subjects in 4 multiple dose studies) (See Appendix 1, pp. 111-113). The following factors were found to be statistically significant:

- Gender: Female subjects had about 14% lower Cmax after single dose administration and somewhat longer terminal T1/2 (14 vs. 11.3 hrs after single dose) than male subjects.
- Race: Mean AUC was higher and mean CL/F 17% lower in Blacks as compared to Caucasians.

Comment:
Since the studies included in the meta analysis were not identical in study design, the analysis provides a clue to potential differences but they need further investigation for confirmation.

Reduced Renal Function

1. Healthy Elderly Subjects with Reduced Renal Function (Study 010)

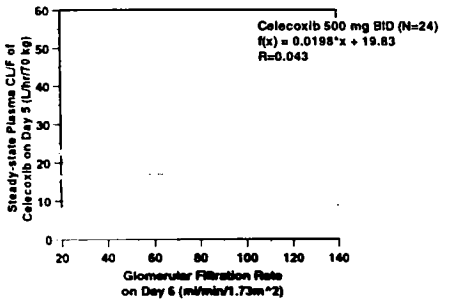
This was a single-blind, randomized, two-period crossover in healthy elderly subjects (GFR and 24 subjects (8 male, 16 female completed the study. One of the treatments in this study was celecoxib 200 mg BID for five days, followed by celecoxib 400 mg BID for five days. All doses were given with food and a washout period of seven days separated each period of study. Blood samples were collected up to 12 hours after morning dose on Days 5 and 10 of each period.

The mean pharmacokinetic parameter values are tabulated below. The steady-state pharmacokinetics of celecoxib after 200 mg BID dosing in this study were relatively consistent with previous findings for healthy elderly subjects in a phase I study (Study 015). Increases in mean steady-state AUC(0-12) and C_{max} of celecoxib were approximately proportional to increases in BID doses between the 200 mg and 400 mg doses.

Multiple-dose Pharmacokinetic or Renal Function Parameter	Treatment Mean (CV)	
	Celecoxib 200 mg BID for 5 Days (Day 5) (N=24)	Celecoxib 400 mg BID for 5 Days (Day 10) (N=24)
AUC(0-12) (hr·ng/ml)	10313 (34%)	20027 (34%)
C_{max} (ng/ml)	1588 (37%)	2824 (31%)
$C_{min(0)}$ (ng/ml)	596.6 (41%)	1362 (53%)
T_{max} (hr)	3.29 (37%)	3.75 (30%)
Plasma CL/F (L/hr/70 kg)	21.32 (32%)	21.74 (28%)
GFR (ml/min/1.73 m^2)	79.19 (16%)[a]	78.94 (18%)[b]

[a]GFR on Day 1; [b]GFR on Day 6

Compared to elderly males (N=8), the arithmetic mean steady-state celecoxib AUC(0-12) and C_{max} in elderly females (N=16) were 28% and 29% higher, respectively, after 200 mg BID dosing and 18% and 14% higher, respectively, after 400 mg BID dosing. As shown in the figure, there was no apparent relationship between steady-state plasma CL/F of celecoxib on Day 5 and GFR during a 1.5 hour period on Day 6 (average of individual GFR measurements at 3, 3.5, 4 and 4.5 hr postdose).



Reviewer's comment:
In this study, Celebrex was taken with food, but the results were similar to those from Study 015 (elderly vs. young subjects under fasted conditions).

2. Patients with Chronic Renal Insufficiency (Study 036)

This was a double-blind, randomized, placebo-controlled, parallel group study conducted to evaluate the effect of celecoxib 200 mg BID or naproxen 500 mg BID on renal function in

patients with stable, chronic renal insufficiency Patients with severe renal insufficiency were not evaluated in this study. Twenty-two patients (11 male, 11 female completed the study. First and last BID doses were given under fasted conditions; all other BID doses were given with food. Blood samples for pharmacokinetic assays were collected for 9 and 72 hours after first and last BID doses, respectively.

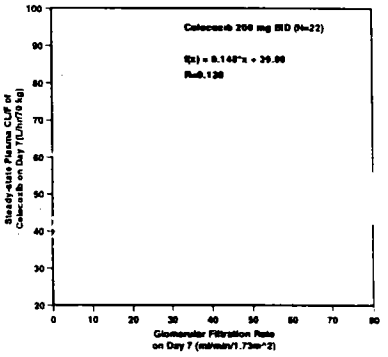
Celecoxib pharmacokinetic results are summarized in the table below. Arithmetic mean steady-state plasma CL/F and drug exposure (AUC) of celecoxib were about 47% higher and 43% lower in patients with chronic renal insufficiency when compared with previous findings for subjects with normal renal function in four multiple-dose phase I studies (Appendix 1, p. 113).

Study 036

Single-dose or Steady-state Celecoxib Pharmacokinetic or Renal Function Parameter	Treatment Mean (CV) [Range] Celecoxib 200 mg BID (N=22)
Celecoxib 200 mg Single Dose (Day 1)	
AUC(0-9) (hr·ng/ml)	2457 (50%)
C_{max} (ng/ml)	508.7 (62%)
T_{max} (hr)	4.50 (41%)
Serum Creatinine (mg/dl)	1.35 (32%)
GFR (-1 to 0 hr) (ml/min/1.73 m^2)	36.7 (42%)
GFR (0 to 3 hr) (ml/min/1.73 m^2)	33.3 (38%)
After Celecoxib 200 mg BID for 7 Days (Day 7)	
AUC(0-12) (hr·ng/ml)	5003 (31%)
$C_{max(0-12)}$ (ng/ml)	662.1 (45%)
$C_{min(0)}$ (ng/ml)	356.0 (47%)
$T_{max(0-12)}$ (hr)	4.27 (61%)
CL/F[d] (L/hr/70 kg)	41.5 (44%)
Terminal T1/2 (hr)	13.1 (52%)
GFR[a] (0 to 3 hr) (ml/min/1.73 m^2)	32.0 (42%)

[a]GFR was the average of individual measurements: predose at -1, -0.5 and 0 hr; and postdose at 0, 0.5, 1, 1.5, 2, 2.5 and 3 hr.
[b]N=21 ; [c]N=20

As shown in the figure, there was no apparent relationship between steady-state plasma CL/F of celecoxib on Day 7 and GFR during a three-hour period on Day 7 (average of individual GFR measurements at 0, 0.5, 1, 1.5, 2, 2.5 and 3 hr postdose).



Reviewer's comment:

The findings suggests lower celecoxib plasma levels in patients with moderate renal insufficiency. This may be caused by decreased protein binding. However, unbound fraction was not determined in this study to support this explanation. Since this study was not provided in the original submission, the review of the detailed report is still ongoing.

Patients with Hepatic Impairment (Study # 016)

This study evaluated the effect of hepatic impairment on the single-dose and steady-state pharmacokinetics of celecoxib. Healthy volunteers with normal hepatic function (n=23) were matched with patients with mild (n=12) or moderate (n=11) hepatic impairment (as determined by the Child-Pugh classification system) by gender, age and weight. MEGX (monoethylglycinexylidide) data comparison for mildly and moderately hepatically impaired subjects support the Child-Pugh system for hepatic impairment classification employed for this study.

Each subject received a single oral dose of celecoxib 100 mg, followed by celecoxib 100 mg BID dosing. Blood and urine samples for pharmacokinetic assay were collected at predetermined intervals for 72 hours after single dose and last BID dose. The detailed study design is given in Appendix 1 (p. 114).

Patients with mild hepatic impairment vs. normal subjects:
Subjects with mild hepatic impairment had higher mean plasma concentrations than normal subjects following single dose administration (Day 1) and at steady state (Day 8). The mean pharmacokinetic parameter values following a single dose and at steady state are tabulated below. A comparison of parameter values between normal and hepatic impairment patients indicated similar trend after a single dose and at steady state.

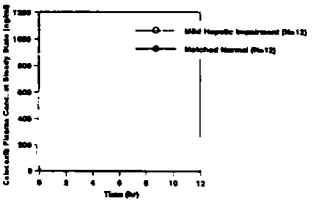


Fig.: Concentration-Time Profile (Day 8)

At steady state, patients with mild hepatic impairment had a 22% lower mean apparent oral clearance (CL/F), a 27% greater AUC(0-12) and a 43% higher Cmax after BID dosing. The difference in CL/F and AUC were not statistically significant but the difference in mean C_{max} was significant. Mean steady-state T_{max} and post steady-state terminal T1/2 of celecoxib were comparable between these patients and normal controls.

Less than 1% of the administered dose was excreted in urine as unchanged celecoxib in patients with mild hepatic impairment and normal control subjects. Steady-state urinary excretion of metabolite, SC-62807 (M2), was statistically significantly higher in mildly-impaired patients than in control subjects (33% vs. 19% of dose, respectively).

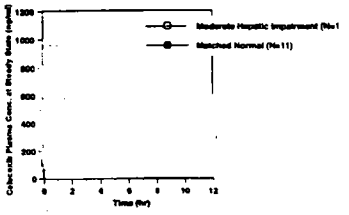
Table: Mild Hepatic Impairment vs. Normal

Celecoxib Pharmacokinetic Parameter	Treatment Group Mean (CV)[a]		Ratio[b]	95% Confidence Interval for Ratio[(b)]
	Mild Hepatic Impairment (N=12)	Normal Control (N=12)	Mild Hepatic/ Normal	
After Single Oral Dose of Celecoxib 100 mg (Day 1)				
AUC(0-72) (hr·ng/ml)	3791 (57%)	2999 (36%)	115.7%	(83.9%, 159.7%)
C_{max} (ng/ml)	525.6 (46%)	342.2 (37%)	147.5%	(97.2%, 223.7%)
T_{max} (hr)	2.17 (47%)	2.17 (47%)	-	-

Terminal T1/2 (hr)	11.2 (47%)	10.8 (27%)[d]	-	-
CL/F (L/hr)[d]	34.5 (48%)	37.1 (35%)	86.4%	(62.6%, 119.2%)
Celecoxib XU(0-72)(mg)	0.004 (248%)	0.002 (181%)	84.7%	(1.7%, 4153.6%)
M2 XU(0-72) (mg)	28.5 (39%)	19.5 (55%)	154.2%	(98.0%, 242.6%)
After Multiple Doses of Celecoxib 100 mg BID (Day 8)				
AUC(0-12) (hr·ng/ml)	3518 (53%)	2575 (33%)	127.4%	(90.5%, 179.3%)
C_{max} (ng/ml)	627.9 (47%)	421.8 (32%)	143.4%	(101.9%, 201.7%)*
$C_{min(0)}$ (ng/ml)	181.4 (79%)	134.0 (56%)	117.7%	(69.3%, 199.9%)
T_{max} (hr)	1.92 (47%)	2.08 (43%)	-	-
Terminal T1/2 (hr)	11.0 (32%)	10.4 (26%)[e]	-	-
CL/F (L/hr)	35.1 (43%)	42.1 (27%)	78.5%	(55.8%, 110.5%)
CL/F (L/hr/70 kg)	32.9 (46%)	38.0 (28%)	-	-
SC-58635 XU_{0-12} (mg)[c]	0.004 (173%)	0.005 (151%)	50.5%	(8.5%, 300.5%)
M2 XU_{0-12} (mg)[c]	32.7 (46%)	18.9 (28%)	160.9%	(108.3%, 239.1%)

[a]Arithmetic mean [b]Ratio based on geometric means XU: Amount excreted in urine

Patients with moderate hepatic impairment vs. normal subjects:
Following a single oral dose of SC-58635 100 mg, it was apparent that subjects with moderate hepatic impairment had substantially higher plasma concentrations. The same was observed after multiple dosing (See figure). The mean parameter values are tabulated below.



Compared to matched control subjects, patients with moderate hepatic impairment had a statistically significant (63%) reduction in mean steady-state CL/F of celecoxib, which resulted in significant increases in plasma celecoxib levels (increases of 120% and 170% in mean C_{max} and $AUC_{(0-12)}$, respectively). Mean T_{max} were comparable (2.0 hr in patients vs. 1.9 hr in controls) while post steady-state terminal T1/2 was longer in the patients (13.6 hr vs. 10.7 hr). Mean steady-state 12-hour urinary excretion of unchanged celecoxib and metabolite SC-62807 were 67% and 62% higher, respectively, although not statistically significantly different from normal control subjects. (The power for detecting a 20% difference was not given.) No clinically relevant changes from baseline were found in creatinine clearance, SGOT, SGPT and bilirubin in these patients after celecoxib 100 mg BID dosing for 5 days.

Table: Moderate Hepatic Impairment vs. Normal

Celecoxib Pharmacokinetic Parameter	Treatment Group Mean (CV)[a]		Ratio[b]	**95% Confidence Interval for Ratio**
	Moderate Hepatic Impairment (N=11)	**Normal Control (N=11)**	**Mod. Hepatic/ Normal**	
After Single Oral Dose of Celecoxib 100 mg (Day 1)				
AUC(0-72) (hr·ng/ml)	6554 (38%)	2663 (31%)	234.2%	(159.1%, 344.9%)*
C_{max} (ng/ml)	458.6 (31%)	325.8 (40%)	146.2%	(97.1%, 220.2%)
T_{max} (hr)	2.77 (82%)	2.91 (42%)	80.6%	(48.8%, 133.2%)
Terminal T1/2 (hr)	14.0 (31%)	11.0 (23%)[d]	129.0%	(97.0%, 171.4%)
CL/F (L/hr)	18.8 (60%)	40.5 (27%)	42.7%	(29.0%, 62.9%)*
SC-58635 $XU_{(0-72)}$ (mg)	0.003 (107%)	0.002 (191%)	129.1%	-
SC-62807 $XU_{(0-72)}$ (mg)	31.1 (40%)	19.9 (48%)	161.8%	(99.3%, 263.4%)

After Multiple Doses of Celecoxib 100 mg BID (Day 8)				
AUC(0-12) (hr·ng/ml)	6458 (41%)	2288 (33%)	269.8%	(194.3%, 374.8%)*
C_{max} (ng/ml)	951.6 (37%)	424.8 (34%)	219.9%	(167.3%, 289.1%)*
$C_{min(0)}$ (ng/ml)	487.4 (53%)	112.6 (50%)	402.9%	(233.8%, 694.2%)*
T_{max} (hr)	2.00 (55%)	1.91 (37%)	-	-
Terminal T1/2 (hr)	13.6 (41%)	10.7 (29%)[d]	122.5%	(93.0%, 161.4%)
CL/F (L/hr)	19.9 (72%)	49.5 (44%)	37.1%	(26.7%, 51.5%)*
CL/F (L/hr/70 kg)	16.2 (77%)	43.4 (43%)	-	-
SC-58635 XU(0-12) (mg)	0.007 (114%)[d]	0.004 (145%)	166.9%	(11.4%, 2451.6%)
SC-62807 XU(0-12) (mg)	31.5 (63%)[d]	16.9 (45%)	162.3%	(90.3%, 291.8%)

[a]Arithmetic mean [b]Ratio based on geometric means XU: Amount excreted in urine

Conclusion:

- Total plasma clearance of SC-58635 after single and multiple dosing was 22% and 63% lower in mildly and moderately hepatically impaired subjects relative to their matched normal subjects; this difference was statistically significant for the moderately hepatically impaired group comparison.
- The AUC and C_{max} values were statistically greater for the moderately hepatically impaired subjects compared to their matched normal subjects.
- Only C_{max} was statistically different for the mildly hepatically impaired subjects compared to their matched normal subjects following multiple dosing.

Reviewer's comment: Patients with severe hepatic impairment were not studied.

DRUG-DRUG INTERACTIONS

Celecoxib is highly plasma protein bound and extensively metabolized after oral administration. Previous experiences indicate that NSAIDs may affect the renal function and alter the pharmacokinetics of drugs that are eliminated mostly by the kidney. Therefore, the drug-drug interaction studies for celecoxib were conducted based on considerations of potential plasma protein binding displacement, inhibition of metabolism and reduction of renal excretion.

In Vitro Studies (Report M3097243)

Celecoxib was examined for its ability to inhibit cytochrome P450 (CYP) isoform-specific catalytic activities associated with CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In vitro interactions were tested by incubating marker substrates with human liver microsomes in the presence of celecoxib or CYP isoform-selective chemical inhibitors, providing initial predictive information on the potential for drug-drug interactions.

The Ki values for both celecoxib and isoform selective inhibitors are tabulated below. The results indicate that :

- Celecoxib is not a potent in vitro inhibitor of CYP2C9, CYP2C19 or CYP3A4, and has low potential to inhibit the metabolism of substrates mediated by these P450 isozymes.
- Celecoxib appears to be a moderately potent in vitro inhibitor of CYP2D6, though approximately 10-fold less potent than the known CYP2D6 inhibitor, quinidine.

CYP Isoform	Marker Activity	Inhibitor	Apparent Ki (μM)
CYP2C9	Tolbutamide 4-Hydroxylation	Celecoxib Sulphaphenazole	44.4 0.585
CYP2C19*	S-Mepheytoin 4'-Hydroxylation	Celecoxib Omeprazole	17.8 5.64
CYP2D6	Bufuralol 1'-Hydroxylation	Celecoxib Qunidine	4.19 0.466
CYP3A4	Testosterone 6β-hydroxylation	Celecoxib Ketoconazole	106 0.0483

Note: Pooled (N = 8) human liver microsomes were used in the study except for CYP2C19.

Reviewer's comment:
The sponsor concluded that the apparent Ki (4.19 μM or 1.6 μg/mL) for the inhibition of CYP2D6 by celecoxib is approximately 3-fold higher than clinical plasma concentrations achieved after 200 and 400 mg/day doses (100 and 200 mg b.i.d., respectively) and, therefore, celecoxib at the recommended doses is not expected to substantially inhibit the metabolism of other drugs that are metabolized via the 2D6 isozyme. It should be noted that elderly subjects (the expected OA population) tend to have higher plasma celecoxib levels. In study 015, 2 elderly subjects had very high plasma concentrations (steady state Cmax of 3.2 and 10.2 μg/mL, respectively). Even after excluding these 2 subjects, 4 out of the 22 (18%) elderly in this study had Cmax greater than the Ki value. Therefore, the potential for a drug-drug interaction with CYP2D6 substrate in vivo cannot be neglected.

In Vivo Studies:

Fluconazole (Study 072)

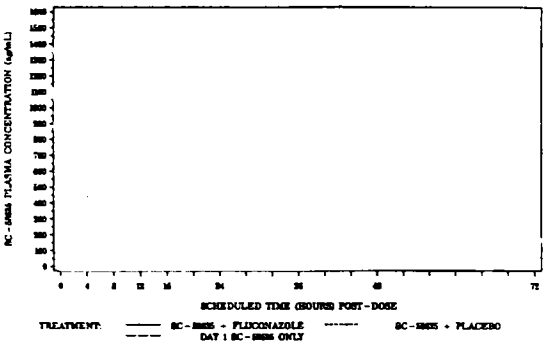
Study 072 was designed to examine the effect of two inhibitors (fluconazole and ketoconazole) on the pharmacokinetics of celecoxib in two parallel groups of healthy volunteers. The fluconazole group will be discussed first.

Fluconazole has been reported to inhibit the metabolism of CYP2C9 substrate and, therefore, may also inhibit the metabolism of celecoxib. The fluconazole group was designed to examine the effect of multiple dosing of fluconazole on the single dose pharmacokinetics of celecoxib and to assess the safety and tolerability of the coadministration. Seventeen healthy subjects in fluconazole group completed the study. On Day 1, subjects received a single dose of celecoxib 200 mg alone. On Days 10 and 19, subjects were administered celecoxib 200 mg as a single dose at the same time as the fluconazole dose. On Days 4-10, subjects were randomized to receive either fluconazole 200 mg QD or placebo. On Days 13-19, subjects were crossed over to receive the

alternate treatment of placebo or fluconazole 200 mg QD. Plasma concentrations of celecoxib and its metabolites (SC-60613 & SC-62807) were determined along with urine excretion of celecoxib and SC-62807 (M2). The detailed study design is given in Appendix 1 (p. 121).

Plasma fluconazole concentrations: On Days 10 and 19, mean plasma fluconazole concentrations reached a maximum of 11.42 (±1.8) ng/mL at 2 hrs postdose and decreased to 3.57 (±0.9) ng/mL at 72 hrs postdose. Mean trough plasma fluconazole concentrations ranged from , on Days 7-10 and from for Days 16-19. A steady state condition could not be confirmed due to a rising trend in trough levels.

Plasma concentrations and urinary excretion of celecoxib: The mean plasma celecoxib concentration-time profiles at baseline (Day 1) and after coadministration with placebo or fluconazole are shown in the figure. Subjects receiving placebo had mean plasma concentrations similar to the baseline values. Coadministration with fluconazole resulted in much higher plasma celecoxib concentrations with an increase of 68% in Cmax and 134% in AUC_{inf} when compared to the placebo treatment. Mean half-life of celecoxib increased The amount of celecoxib excreted unchanged renally within 72 hrs postdose increased These results suggested that fluconazole inhibit the metabolism of celecoxib.



Mean Celecoxib Parameter Values (±SD)

Parameter	Celecoxib (Baseline)	Celecoxib + Fluconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	7991.6 ± 2548.0	16792.9 ± 5058.7**	7282.5 ± 2758.1
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	7731.6 ± 2408.5	16496.9 ± 5155.7 **	7054.9 ± 2799.5
$AUC_{0\text{-}inf}$ (ng.hr/mL)	8133.5 ± 2679.2	17103.8 ± 5424.0**	7397.3 ± 2819.7
C_{max} (ng/mL)	735.3 ± 289.0	1038.7 ± 377.3*	649.0 ± 322.0
T_{max} (hrs)	2.9 ± 1.3	3.4 ± 1.6	2.6 ± 0.8
$T_{½}$ (hrs)	9.8 ± 3.7	11.2 ±3.1	9.6 ± 2.5
$XU_{0\text{-}72\ hr}$ (μg)	4.42 ± 8.62	23.66 ± 21.27	7.51 ± 11.1

*p<0.05; **p<0.001; based on comparison of (celecoxib + fluconazole) vs. (celecoxib + placebo)

Plasma concentrations of metabolite SC-60613: Mean peak plasma concentration of SC-60613 was reached at 2 hours postdose and was below the level of quantitation (<0.100 ng/mL) at 72 hrs postdose. When compared to the celecoxib+placebo treatment, celecoxib+ fluconazole treatment resulted in a decrease of 51.5% in Cmax and 19.3% in AUC_{inf} (see Table below). Analysis of variance indicated that there was a statistically significant difference between

coadministration with placebo and coadministration with fluconazole for both AUC and Cmax (α=0.05).

Plasma concentrations and urinary excretion of metabolite SC-62807: The mean plasma concentration of SC-62807 reached a maximum at approximately 3 hours postdose and decreased to <10 ng/mL at 72 hrs postdose. When celecoxib was coadministered with fluconazole, mean Cmax decreased appreciably (44%) but there was not much change in mean AUC_{0-72} or AUC_{inf}. The amount of SC-62807 excreted in the urine from 0-72 hours postdose were comparable between the two treatments, however, it is noted that the excretion rate in the first 24 hours postdose was significantly lower (18%; p=0.030) for celecoxib+fluconazole (1300±517 μg/hr) than for celecoxib+placebo (1579±559 μg/hr).

Parameter	Celecoxib (Baseline)	Celecoxib + Fluconazole	Celecoxib + Placebo
SC-60613			
$AUC_{0-72\ hr}$ (ng.hr/mL)	461.5 ± 118.3	261.1 ± 87.0 **	348.8 ± 87.1
AUC_{0-lqc} (ng.hr/mL)	446.9 ± 117.6	246.4 ± 85.1**	336.9 ± 87.3
AUC_{0-inf} (ng.hr/mL)	471.5 ± 123.3	293.2 ± 81.0**	363.1 ± 84.7
C_{max} (ng/mL)	78.2 ± 30.4	25.8 ± 9.4 **	53.2 ± 19.2
T_{max} (hrs)	2.4 ± 1.1	2.2 ± 0.7	2.1± 0.8
$T_{½}$ (hrs)	9.4 ± 3.6	15.7 ± 5.7	11.6 ± 5.7
SC-62807			
Parameter	Celecoxib (Day 1)	Celecoxib + Fluconazole	Celecoxib + Placebo
$AUC_{0-72\ hr}$ (ng.hr/mL)	5407.2 ± 1406.9	4990.3 ± 1235.1	4887.7 ± 1226.7
AUC_{0-lqc} (ng.hr/mL)	5378.4 ± 1401.1	4990.3 ± 1235.1	4864.6 ± 1232.1
AUC_{0-inf} (ng.hr/mL)	5687.5 ± 1168.4	5224.5 ± 1412.3	5085.3 ± 1286.7
C_{max} (ng/mL)	641.9 ± 375.3	287.5 ± 121.8**	504.3 ± 235.6
T_{max} (hrs)	3.1 ± 0.8	3.9 ± 1.3	3.0 ± 0.7
$T_{½}$ (hrs)	11.9 ± 4.2	14.2 ± 5.8	12.1 ± 3.1
$XU_{0-72\ hr}$ (μg)	47565 ± 12058	45946 ± 14794	46953 ± 13008

**p<0.001

Conclusion:
Coadministration of fluconazole inhibits the metabolism of celecoxib and resulted in an increase of 60.0% in Cmax and 131.2% in AUC_{inf}.

Reviewer's comments:
1. It takes up to 10 days to reach steady state for fluconazole after QD dosing. The 7-day dosing for this study appeared inadequate to reach steady state fluconazole levels.
2. The decrease in Cmax for metabolites SC-60613 and SC-62807 supports the notion that fluconazole inhibits the metabolism of celecoxib.

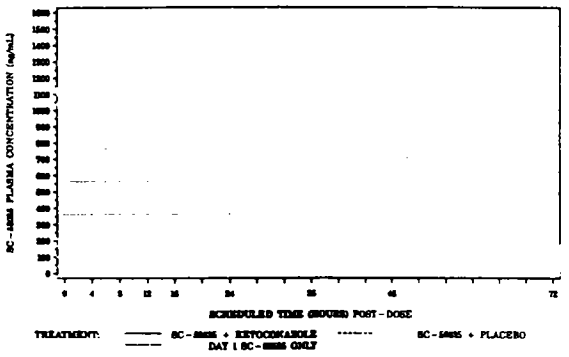
Ketoconazole (Study 072)

Ketoconazole is a potent CYP3A4 inhibitor. As part of Study 072, single dose pharmacokinetics of celecoxib was determined in the presence and absence of steady

state levels of ketoconazole following 200 mg QD administration. The study design is similar to that for fluconazole and can be found in Appendix 1 (p. 121). Eighteen healthy subjects completed the study.

Plasma ketoconazole concentrations: On Days 10 and 19, mean plasma ketoconazole concentrations reached a maximum of 3.36 (±1.29) ng/mL at 2 hrs postdose and decreased to 0.01 ng/mL at 72 hrs postdose, which were consistent with published data. Steady state was reached on celecoxib dosing days (Days 10 and 19).

Plasma celecoxib concentrations:
Following a single dose of celecoxib 200 mg alone, mean peak plasma celecoxib concentration (538.6 ±231.9 ng/mL) was reached at 2.5 hrs postdose. As shown in the figure, coadministration of celecoxib with ketoconazole or placebo gave similar plasma celecoxib concentration-time profiles.



Because one subject (#031) had high plasma levels of celecoxib before the first celecoxib dose, the mean parameter values for celecoxib as tabulated below excluded this subject. Based on least square means of log-transformed parameters, subjects receiving celecoxib with ketoconazole had a 10% higher mean AUC and a 12% lower mean Cmax when compared to subjects receiving celecoxib with placebo. The difference was statistically significant for AUC but not for Cmax. The mean amount of celecoxib excreted unchanged renally remained within the range following coadministration with ketoconazole.

Mean Celecoxib Parameter Values (±SD)

Parameter (n=17)	Celecoxib (Baseline)	Celecoxib + Ketoconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	7699.1 ± 2184.8	7698.3 ± 2318.5*	7065.6 ± 2517.8
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	7475.9 ± 2180.2	7453.7 ± 2300.3*	6836.5 ± 2480.5
$AUC_{0\text{-}inf}$ (ng.hr/mL)	7914.9 ± 2174.6	7850.5 ± 2294.0*	7211.0 ± 2493.5
C_{max} (ng/mL)	596.5 ± 231.9	567.4 ± 320.3	614.9 ± 214.0
T_{max} (hrs)	2.5 ± 0.9	3.5 ± 1.9	2.8 ± 0.9
$T_{½}$ (hrs)	12.2 ± 2.6	11.2 ±3.3	11.0 ± 3.6
$XU_{0\text{-}72\ hr}$ (μg) (n=6)	19.5 ± 23.3	17.8 ± 22.6	12.5 ± 21.9

*p<0.05; based on a comparison of (celecoxib + ketoconazole) vs. (celecoxib + placebo)

Plasma concentrations of metabolites SC-60613 & SC-62807: Based on least square means of log-transformed parameter values, decreases in C_{max} of metabolites SC-60613 (35%) and SC-62807 (37%) and SC-62807 $AUC_{(0\text{-}\infty)}$ (10%) after ketoconazole+celecoxib were statistically significantly different from placebo coadministration. The 11% decrease in SC-60613 $AUC_{(0\text{-}\infty)}$ did not demonstrate statistical significance. Excretion of SC-62807 in 72-hour urine after ketoconazole+celecoxib was 17% lower, but not significantly different from placebo.

Table: Mean (±SD) Parameter Values

Parameter	Celecoxib (Baseline)	Celecoxib + Ketoconazole	Celecoxib + Placebo
SC-60613			
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	457.6 ± 112.1	333.0 ± 87.7*	385.0 ± 103.7
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	436.1 ± 110.1	317.2 ± 87.3	368.6 ± 100.6
$AUC_{0\text{-}inf}$ (ng.hr/mL)	487.6 ± 103.9	363.7 ± 74.5	411.3 ± 105.7
C_{max} (ng/mL)	65.6 ± 18.9	38.5 ± 11.6*	58.5 ± 15.0
T_{max} (hrs)	2.2 ± 0.7	2.9 ± 0.8	2.2 ± 0.8
$T_{½}$ (hrs)	13.6 ± 4.5	14.3 ± 7.1	12.0 ± 4.5
SC-62807			
Parameter	Celecoxib (Day 1)	Celecoxib + Ketoconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	6554.7 ± 1737.4	4990.3 ± 1235.1*	4887.7 ± 1226.7
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	6543.1 ± 1725.8	4990.3 ± 1235.1*	4864.6 ± 1232.1
$AUC_{0\text{-}inf}$ (ng.hr/mL)	6764.8 ± 1722.3	5224.5 ± 1412.3*	5085.3 ± 1286.7
C_{max} (ng/mL)	594.1 ± 286.6	287.5 ± 121.8**	504.3 ± 235.6
T_{max} (hrs)	3.2 ± 1.0	3.9 ± 1.3	3.0 ± 0.7
$T_{½}$ (hrs)	14.3 ± 4.3	14.2 ± 5.8	12.1 ± 3.1
$XU_{0\text{-}72\ hr}$ (μg)	56342 ± 13904	45946 ± 14794	46953 ± 13008

*$p < 0.05$ based on a comparison of (celecoxib + ketoconazole) vs. (celecoxib + placebo)

Conclusion:

Based on plasma metabolite data, ketoconazole might inhibit celecoxib metabolism as well. However, the inhibition was considerably less for ketoconazole than for fluconazole. These results confirmed the in vitro finding that CYP2C9 was the primary isozyme involved in celecoxib metabolism.

Reviewer's comments:

1. Subject (#031) had high plasma levels of celecoxib before the first celecoxib dose (Day 1) and, therefore, was excluded from the analysis. The sponsor suspected assay interferences. It is noted that this subject had consistently high plasma celecoxib levels after each of the three doses given on Days 1, 10 and 19 and the Cmax for this subject was about 10-fold that of the mean value. It is also noted that on Days 10 and 19, the pre-dose level for this subject was either near or below the Assay interferences did not seem to fully explain the high celecoxib levels in this subject. However, including this subject in the analysis did not change the overall conclusion.
2. Ketoconazole might inhibit celecoxib metabolism as well but the inhibition appeared to be transient in nature (i.e. when ketoconazole plasma concentrations were near the peak).

Methotrexate (Study 017)

Methotrexate is indicated in the management of severe, active rheumatoid arthritis in patients who have had insufficient response to, or are intolerant of, other treatments including NSAIDs. Urinary excretion is an important route of elimination for this drug. The primary objective of this study was to determine the effect of celecoxib on the plasma pharmacokinetic profile and renal clearance of methotrexate (MTX) in rheumatoid arthritis patients. Fourteen female patients who were on a stable weekly dose